



S I G N

SIGN Publication
Number

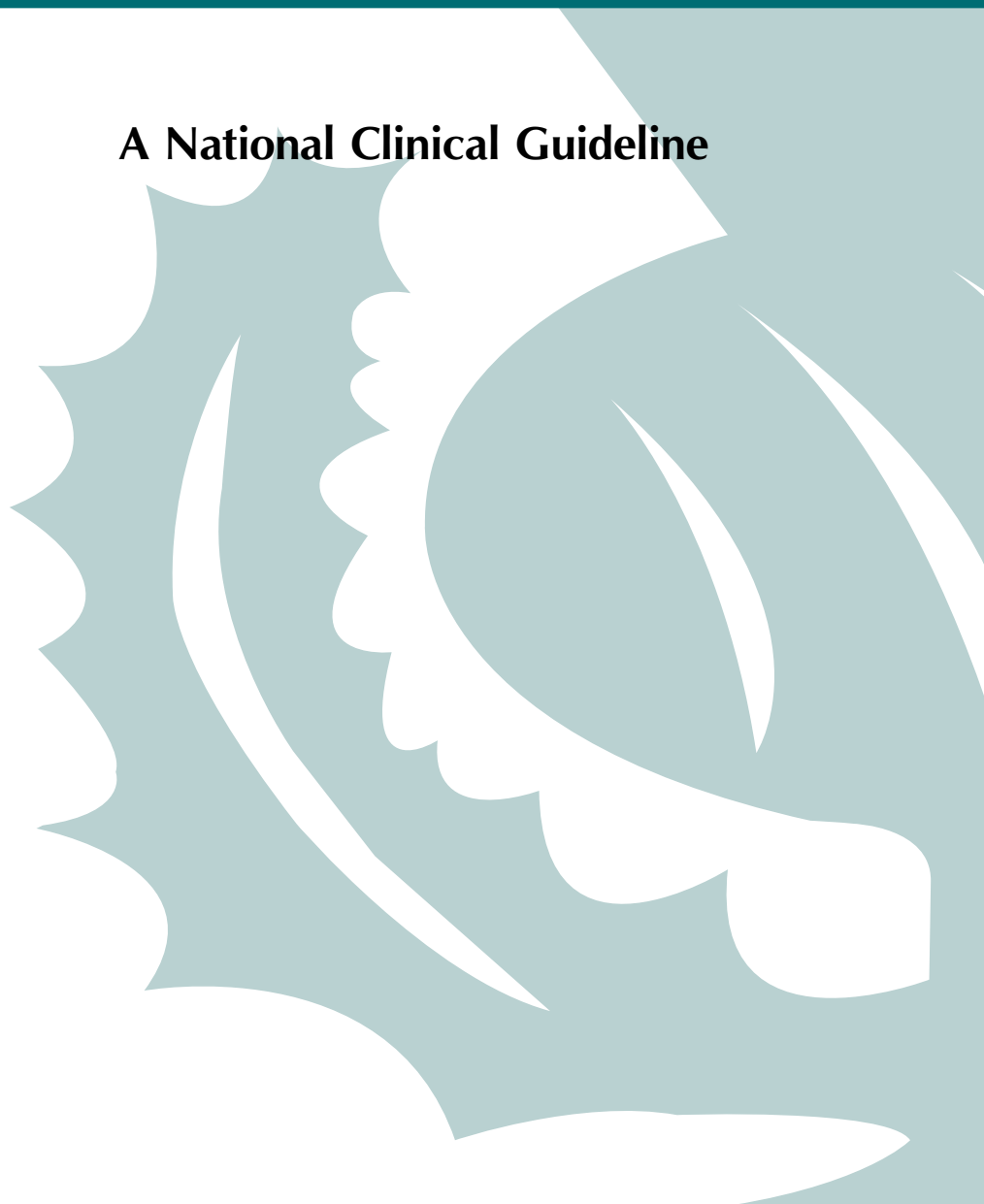
48

Scottish
Intercollegiate
Guidelines
Network

Management of Early Rheumatoid Arthritis

A National Clinical Guideline

December 2000



KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

STATEMENTS OF EVIDENCE

1 ⁺⁺	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 ⁺	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 ⁻	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2 ⁺⁺	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2 ⁺	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 ⁻	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATIONS

A	At least one meta-analysis, systematic review, or RCT rated as 1⁺⁺, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1⁺, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2⁺⁺, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1⁺⁺ or 1⁺
C	A body of evidence including studies rated as 2⁺, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2⁺⁺
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2⁺

GOOD PRACTICE POINTS

<input checked="" type="checkbox"/>	Recommended best practice based on the clinical experience of the guideline development group
-------------------------------------	---

Contents

<i>Guideline development group</i>	_____	(i)
<i>Notes for users of the guideline</i>	_____	(iii)
<i>Abbreviations</i>	_____	(iv)
<i>Summary of recommendations</i>	_____	(v)
1	Introduction	
1.1	Background _____	1
1.2	The need for a guideline _____	1
1.3	Remit _____	1
1.4	Grading of recommendations _____	1
2	Diagnosis of early rheumatoid arthritis	
2.1	Clinical features _____	2
2.2	Investigation _____	2
2.3	Prognostic features in early RA _____	4
3	Principles of treatment	
3.1	Early initiation of treatment _____	5
3.2	Multidisciplinary team approach _____	5
3.3	Patient education _____	5
3.4	Assessment of response to treatment _____	5
3.5	Hospital admission _____	6
3.6	Cost of untreated disease _____	6
4	Pharmacological management	
4.1	Analgesics _____	7
4.2	Nonsteroidal anti-inflammatory drugs (NSAIDs) _____	7
4.3	Disease modifying anti-rheumatic drugs (DMARDs) _____	10
4.4	Targeted immunotherapy _____	14
4.5	Intra-articular corticosteroids _____	14
4.6	Systemic corticosteroids – oral and parenteral _____	15
4.7	Complementary medicine _____	17
4.8	Other therapies _____	17
5	The role of the multidisciplinary team	
5.1	Occupational therapy _____	18
5.2	Physiotherapy _____	18
5.3	Splinting _____	19
5.4	Podiatry _____	19
5.5	Dietetics _____	19

Annexes

1	<i>Details of systematic review undertaken for the guideline</i>	21
2	<i>American Rheumatism Association 1987 revised criteria for the classification of RA</i>	22
3	<i>Criteria for complete remission in RA</i>	23
4	<i>Health assessment questionnaire</i>	24
5	<i>Evaluation of DMARD effect</i>	26
6	<i>Drug interactions with NSAIDs and DMARDs</i>	27
7	<i>Extent of response to single agents in recent DMARD studies</i>	28
8	<i>Recommendations for further research</i>	29
9	<i>Key messages for patients</i>	31
10	<i>Example patient information leaflet</i>	32
11	<i>Useful organisations/support groups</i>	35

References		37
-------------------	--	----

Tables

1	<i>Assessing a patient presenting with inflammatory arthritis</i>	2
2	<i>Differential diagnosis of early RA</i>	3
3	<i>Investigations helpful in diagnosis of RA</i>	3
4	<i>Risk factors for NSAID associated gastroduodenal ulcers</i>	8
5	<i>Summary of gastroprotective agents in RA</i>	8
6	<i>DMARD profiles</i>	12

GUIDELINE DEVELOPMENT GROUP

Dr Hilary Capell (Chair)	Consultant Rheumatologist, Glasgow Royal Infirmary
Dr Elaine Morrison (Methodologist)	Consultant Physician/Rheumatologist, Southern General Hospital, Glasgow
Mr William Brandon	Patient representative, Glasgow
Mrs Jean Coote	Chief Pharmacist, Royal Alexandra Hospital, Paisley
Mrs Chris Duncan	Senior Occupational Therapist, Ninewells Hospital, Dundee
Miss Fiona Gough	Senior 1 Physiotherapist, Glasgow Royal Infirmary and Lecturer, Caledonian University, Glasgow
Dr Margaret Hannah	Consultant in Public Health, Fife Health Board
Dr Gillian Hosie	General Practitioner, Glasgow
Dr Bangarpet Krishnaswamy	General Practitioner, Glenrothes
Dr Rajan Madhok	Consultant Rheumatologist, Glasgow Royal Infirmary
Dr Nicola Maiden	Specialist Registrar, Western General Hospital, Edinburgh
Sister Darryl McGhee	Nurse Specialist, Southern General Hospital, Glasgow
Professor George Nuki	Consultant Rheumatologist, Western General Hospital, Edinburgh
Dr Paul Rasdale	General Practitioner, Dingwall
Dr Norris Rennie	Consultant Rheumatologist, Aberdeen Royal Infirmary
Dr Malcolm Steven	Consultant Physician/Rheumatologist, Raigmore Hospital, Inverness
Miss Gael Young (resigned)	Patient representative, Strathpeffer
Ms Sharon Wiener-Ogilvie	Podiatrist, Hairmyres Hospital, East Kilbride
Mrs Dania Wood	Dietitian, Glasgow Royal Infirmary

SPECIALIST REVIEWERS

Mrs Amanda Avery	Senior Community Dietitian, Aston Hall Hospital, Derby
Professor Howard Bird	Professor of Pharmacological Rheumatology, University of Leeds
Dr Alan Black	General Practitioner, Kirkcaldy
Dr Adrian Carr	Public Health Research Specialist, Ayrshire and Arran Health Board
Ms Anne Chadwick	Physiotherapy Lecturer/Practitioner (Rheumatology), Keele University
Dr Ross Duff	General Practitioner, Brechin
Mr Brian Ellis	Head of Department of Podiatry and Radiography, Queen Margaret University College, Dunfermline
Dr Andrew Henderson	Consultant Physician, Lorn and Islands District General Hospital, Oban
Ms Jackie Hill	Lecturer/Rheumatology Nurse Practitioner, Leeds
Dr Walter Jamieson	General Practitioner, Edinburgh
Dr Jacqueline McDonald	General Practitioner, Edinburgh
Dr Alistair Noble	General Practitioner, Nairn
Mr George Rendall	Manager Orkney Podiatry Services / Lecturer, Queen Margaret University College, Edinburgh
Ms Sarah Ryan	Clinical Nurse Specialist (Rheumatology), North Staffordshire Hospital
Dr Chris Sharpe	General Practitioner, Selkirk
Dr Deborah Symmons	Clinical Reader in Rheumatic Disease Epidemiology, University of Manchester
Dr Alex Watson	General Practitioner, Dundee
Ms Anne Watson	Principal Pharmacist, Southern General Hospital, Glasgow
Miss Janet Wilson	Head Occupational Therapist, Cameron Hospital, Fife
Ms Deborah Wyles	Community Dietitian, St Lukes Hospital, Bradford

SIGN EDITORIAL BOARD

Professor James Petrie	<i>Chairman of SIGN</i>
Dr Doreen Campbell	<i>CRAG Secretariat, Scottish Executive Department of Health</i>
Dr Patricia Donald	<i>Primary Care Advisor to SIGN</i>
Professor Gordon Lowe	<i>Royal College of Physicians Edinburgh</i>
Ms Juliet Miller	<i>Director of SIGN</i>
Ms Tracy Nairn	<i>Professions Allied to Medicine Advisor to SIGN</i>
Dr Margaret Roberts	<i>Royal College of Physicians & Surgeons of Glasgow</i>
Mr Peter Wimpenny	<i>Centre for Nursing Practice Development, Robert Gordon University, Aberdeen</i>

SIGN EXECUTIVE

Ms Anne Borthwick	<i>Publications Officer</i>
Ms Francesca Chappell	<i>Information Officer</i>
Miss Emer Clifford	<i>Publications Assistant</i>
Ms Gail Crosbie	<i>Networking Coordinator</i>
Dr Ali El-Ghorr	<i>Programme Manager</i>
Mrs Lesley Forsyth	<i>Conferences Coordinator</i>
Mr Robin Harbour	<i>Information Manager</i>
Mr Graeme McAlister	<i>Communications Manager</i>
Ms Paula McDonald	<i>Senior Guideline Coordinator</i>
Ms Juliet Miller	<i>Director</i>
Ms Fiona Moncur	<i>Guideline Coordinator</i>
Dr Moray Nairn	<i>Programme Manager</i>
Mrs Judith Proudfoot	<i>Administrator</i>
Ms Gaynor Rattray	<i>Guideline Coordinator</i>
Dr Safia Qureshi	<i>Senior Programme Manager</i>
Mr Duncan Service	<i>Information Services Officer</i>
Miss Leanne Stirling	<i>Administration Assistant</i>
Ms Joanne Topalian	<i>Programme Manager</i>

Notes for users of the guideline

DEVELOPMENT OF LOCAL GUIDELINES

It is intended that this guideline will be adopted after local discussion involving clinical staff and management. The Area Clinical Effectiveness Committee should be fully involved. Local arrangements may then be made for the derivation of specific local guidelines to implement the national guideline in individual hospitals, units and practices and for securing compliance with them. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

SIGN consents to the copying of this guideline for the purpose of producing local guidelines for use in Scotland.

STATEMENT OF INTENT

This report is not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve.

These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor in light of the clinical data presented by the patient and the diagnostic and treatment options available.

Significant departures from the national guideline as expressed in the local guideline should be fully documented and the reasons for the differences explained. Significant departures from the local guideline should be fully documented in the patient's case notes at the time the relevant decision is taken.

A background paper on the legal implications of guidelines is available from the SIGN executive.

REVIEW OF THE GUIDELINE

This guideline was issued in December 2000 and will be reviewed in 2002 or sooner if new evidence becomes available. Any amendments to the guideline in the interim period will be noted on the SIGN website. Comments are invited to assist the review process. All correspondence and requests for further information regarding the guideline should be addressed to:

SIGN Executive
Royal College of Physicians
9 Queen Street
Edinburgh EH2 1JQ
Tel: 0131 225 7324
Fax: 0131 225 1769

e-mail: sign@rcpe.ac.uk
www.sign.ac.uk

Abbreviations

ACR	American College of Rheumatology
ANA	Antinuclear antibody
ARA	American Rheumatism Association
ARAMIS	Arthritis, Rheumatism and Aging Medical Information System
BMI	Body mass index
Cox	Cyclooxygenase
CRP	C-reactive protein
CT	Connective tissue
DAS	Disease activity score
DMARD	Disease modifying anti-rheumatic drug
EBV	Epstein-Barr virus
ESR	Erythrocyte sedimentation rate
EULAR	European League against Rheumatism
FBC	Full blood count
GI	Gastrointestinal
GP	General Practitioner
HAQ	Health assessment questionnaire
HLA	Human leukocyte antigen
HRT	Hormone replacement therapy
IBD	Inflammatory bowel disorder
IM	Intramuscular
LFT	Liver function test
MCP	Metacarpophalangeal
MTP	Metatarsophalangeal
NNT	Number needed to treat
NSAID	Nonsteroidal anti-inflammatory drug
OT	Occupational therapy
PIP	Proximal interphalangeal
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RF	Rheumatoid factor
SC	Subcutaneous
SIGN	Scottish Intercollegiate Guidelines Network
SLE	Systemic lupus erythematosus
SSRI	Selective serotonin re-uptake inhibitor
TENS	Transcutaneous electrical nerve stimulation
TNF	Tumour necrosis factor
U&E	Urea & electrolytes

Summary of recommendations

TREATMENT OVERVIEW

B RA should be treated as early as possible with disease modifying anti-rheumatic drugs (DMARDs) to control symptoms and delay disease progression.

- All patients with persistent inflammatory joint disease (> 6-8 weeks duration) already receiving simple analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) should be considered for referral for specialist rheumatology opinion and DMARD therapy, preferably within 12 weeks.
- Patient education should be undertaken by all members of the multidisciplinary teams in both primary and secondary care.
 - Patients should be provided with an information leaflet/booklet, and if possible, one-to-one education.

NSAIDs

B The lowest NSAID dose compatible with symptom relief should be prescribed.

NSAIDs should be reduced and if possible withdrawn when a good response to DMARDs is achieved.

- Simple analgesics should be used in place of NSAIDs if possible and DMARDs should be introduced early to suppress disease activity.
 - Only one NSAID should be prescribed at a time.
 - Prescribers should be aware of the many potential drug interactions with NSAIDs and the side effect profiles of different drugs.
 - NSAIDs should be avoided in patients taking anticoagulants or corticosteroids.

B Introduce gastroprotection in RA patients > 65 years and in those with a past history of peptic ulcer.

DMARDs

B Early DMARD therapy in RA is important to maintain function and reduce later disability.

DMARD therapy should be sustained in inflammatory disease in order to maintain disease suppression.

- DMARD choice should take into account patient preference and existing co-morbidity.

B Sulphasalazine, methotrexate, IM gold, and pencillamine are equally effective DMARDs.

Sulphasalazine and methotrexate are the current DMARDs of choice due to their more favourable efficacy/toxicity profiles.

- Patients should be counselled about the benefits and risks of specific DMARDs, and should be provided with additional written information.
 - Good liaison between primary and secondary care is essential. Rheumatology nurse specialists have an important role in this aspect of care.
 - Monitor for continued efficacy (ESR/CRP, number of tender and swollen joints, duration of morning stiffness, function).

- Monitor toxicity using British Society of Rheumatology/local guidelines or manufacturers' data sheet recommendations.
 - Clear advice about the monitoring of specific DMARDs should be available to the patient, GP and practice nurse.

B At present the balance of evidence does not support the routine use of combination DMARD therapy in early RA.

INTRA-ARTICULAR CORTICOSTEROIDS

- Intra-articular injections can be used for rapid, and sometimes sustained, symptomatic relief in 'target' joints.
 - Intra-articular injections to any one joint should not be given more than three times in one year.
 - When administering intra-articular injections:
 - use sterile technique
 - advise patients how to seek help if joint fails to settle after injection
 - always consider possible septic arthritis in differential diagnosis of mono/oligo flare in RA.

CORTICOSTEROID THERAPY

B Oral corticosteroids are not recommended for routine use, as there is no sustained clinical or functional benefit and there is a high risk of toxicity with long term use.

- Inform patients of the risks of corticosteroids prior to prescription and issue a steroid warning card.
 - Intramuscular corticosteroid allows control of dose and duration of therapy and may be preferable to oral therapy.
 - Oral corticosteroids should be withdrawn slowly to avoid rebound flare of symptoms.

D The lowest possible dose of corticosteroid should be used for the shortest possible time.

Monitor patients closely for adverse corticosteroid effects. Be alert to the possibility of diabetes, cataract and infection. Inform patients not previously infected of the danger of chicken pox/shingles exposure.

- Ensure adequate prophylaxis and treatment of osteoporosis in patients taking oral corticosteroids.

THE ROLE OF THE MULTIDISCIPLINARY TEAM

- All patients with early RA should have access to a range of health professionals, including general practitioner, rheumatologist, nurse specialist, physiotherapist, occupational therapist, dietitian, podiatrist, pharmacist and social worker.

C Skilled occupational therapy advice should be available to those experiencing limitations in function.

Resting and working splints can be used to provide pain relief.

B Patients should be encouraged to undertake simple dynamic exercises.

- Podiatry referral should be offered to all patients.

1 Introduction

1.1 BACKGROUND

Rheumatoid arthritis (RA) affects approximately 1% of the population and is more common in women than in men. The course of RA is variable and unpredictable but for a significant number of patients it is a severe disease resulting in persistent pain and stiffness, progressive joint destruction, functional decline and premature mortality.¹⁻³ Equally important to affected individuals is the potential loss of social and financial independence.⁴

The disease also exerts a considerable burden on society in terms of direct (e.g. medical care) and indirect costs (e.g. effects on the individual's ability to work, see *section 3.6*).^{5,6}

1.2 THE NEED FOR A GUIDELINE

The traditional management of RA, the 'treatment pyramid', begins with mild, mainly symptomatic measures and defers the use of disease modifying drugs until the disease has progressed further. However, increasing recognition that, for many patients, RA is not a benign condition with a good prognosis has prompted a re-evaluation of therapeutic strategies and the clinical effectiveness of the traditional approach has been widely challenged.⁷⁻⁹ It has been shown that erosive change, leading to joint destruction, often occurs in early disease¹⁰⁻¹⁴ and that early loss of function may be irreversible. In addition, evidence is now accumulating that early more aggressive intervention can improve longer term disease outcome.¹⁵ There is therefore a need for an evidence-based guideline for the management of early RA.

1.3 REMIT

This guideline addresses diagnosis of early RA, its pharmacological treatment, and the role of the multidisciplinary team in improving care of the RA patient. It is hoped that the guideline will inform standards for practice for rheumatologists, general practitioners (GPs), rheumatology nurse specialists, physiotherapists, occupational therapists, dietitians, podiatrists and pharmacists.

At present there is no formal definition of 'early RA'. It is defined in this guideline as disease duration of < 5 years from onset of symptoms.

The guideline does not cover:

- Treatment of co-morbidity (e.g. anaemia, osteoporosis)
- Complications of drug therapy and their management
- Treatment of extra-articular disease (e.g. vasculitis, ocular complications, amyloid)
- Surgical intervention
- Management of children with arthritis.

1.4 GRADING OF RECOMMENDATIONS

This guideline introduces for the first time a revised system for grading guideline recommendations. A key to the new grading system is provided on the inside front cover. Further information is available on the SIGN website: www.sign.ac.uk.

2 Diagnosis of early rheumatoid arthritis

Early diagnosis of RA is a prerequisite for early treatment and is not always easy to achieve. Diagnosis relies heavily on history taking and clinical examination and less on investigations.

The American College of Rheumatology (ACR; previously the American Rheumatism Association) criteria for the classification of RA¹⁶ illustrates this (see *Annex 2*). The ACR criteria are, however, primarily a research tool and are much less useful in routine clinical practice.

2.1 CLINICAL FEATURES

A typical patient with early RA will describe pain, stiffness and swelling in the joints that is worse in the morning and after inactivity. Examination (see *Table 1*) reveals symmetrical swelling and tenderness of the small joints of the hands and feet (and to a variable extent the larger joints) and the presence of synovitis (i.e. soft tissue swelling in relation to the joint). Systemic 'flu-like' symptoms are not uncommon. Atypical presentations of RA include patients with mainly girdle joint involvement mimicking polymyalgia rheumatica and those with persistent monoarthritis.

These findings are not, however, exclusive to RA and may occur in a number of other inflammatory arthropathies. In early disease, therefore, differential diagnosis should always be considered (see *Table 2*).

2.2 INVESTIGATION

There is no single diagnostic test for RA. Investigations are used largely to support the clinical diagnosis and negative results do not exclude the diagnosis of RA. Investigations which may be helpful in making the diagnosis of early RA are shown in *Table 3*.

Table 1

ASSESSING A PATIENT PRESENTING WITH INFLAMMATORY ARTHRITIS

Essential aspects of the consultation

History

- pain
- stiffness after inactivity
- joint swelling
- fatigue

Examination

- affected joints
- synovitis vs. bony swelling/deformity
- range of movement
- extra-articular features

Desirable aspects of the consultation

Functional status, e.g. health assessment questionnaire (HAQ)¹⁷

Impact of disease

Social circumstances/depression/anxiety

Table 2

DIFFERENTIAL DIAGNOSIS OF EARLY RA

-
- Viral arthritis (e.g. parvovirus, rubella)
 - Reactive arthritis (e.g. post-infective: throat, gut, sexually acquired)
 - Seronegative spondyloarthropathy (e.g. psoriatic, ankylosing spondylitis, inflammatory bowel disease)
 - Connective tissue disease (e.g. systemic lupus erythematosus (SLE), scleroderma)
 - Polymyalgia rheumatica
 - Polyarticular gout
 - Fibromyalgia
 - Medical conditions presenting with arthropathy (e.g. sarcoidosis, thyroid disease, infective endocarditis, haemochromatosis, diabetic cheiroarthropathy, paraneoplastic syndromes, multiple myeloma).
-

Table 3

INVESTIGATIONS HELPFUL IN DIAGNOSIS OF RA

Investigation	Findings
Erythrocyte sedimentation rate (ESR)/ C-reactive protein (CRP) / plasma viscosity	Usually elevated in RA but may be normal
Full blood count (FBC)	Normochromic, normocytic anaemia and reactive thrombocytosis common in active disease
Urea & electrolytes (U&E), Liver function tests (LFT)	Mild elevation of alkaline phosphatase and gamma-GT common in active disease
Uric acid/ synovial fluid analysis	Will assist in excluding polyarticular gout
Urinalysis	Microscopic haematuria/proteinuria may suggest connective tissue disease
Rheumatoid factor (RF)	RF positive in only 60-70% RA patients. May be positive in other inflammatory diseases and normal individuals
Antinuclear antibody (ANA)	Positive in SLE and related conditions. ANA positive in up to 30% of RF-positive RA patients. May be weakly positive in up to 10% of normal individuals
Radiology	May be normal or may show periarticular osteopenia and/or erosions

2.3 PROGNOSTIC FEATURES IN EARLY RA

Predicting outcome in RA in individual patients at disease outset is difficult. Improved understanding of prognostic features would help to identify patients with serious disease who require aggressive therapy and protect those with mild disease from exposure to potentially toxic treatment. Indicators of poor outcome (radiological, functional, mortality) are:

- many active joints^{18–20}
- high ESR or CRP at outset^{12, 21–23}
- positive rheumatoid factor^{19, 24–26}
- early radiological erosions²⁷
- poorer scores of function (e.g. HAQ) at outset^{18, 19, 28, 29}
- adverse socio-economic circumstances and lower educational level^{30–34}

3 Principles of treatment

3.1 EARLY INITIATION OF TREATMENT

It is well documented that the function of patients with RA will decline over time.³⁵⁻³⁷ The goals of treatment, therefore, are symptom control, reduction of joint damage and disability and maintenance or improvement of quality of life. Whilst current therapies seldom achieve remission, they can slow disease progression and thereby reduce functional loss.

Evidence level 2+

B RA should be treated as early as possible with disease modifying anti-rheumatic drugs (DMARDs) to control symptoms and delay disease progression.

- All patients with persistent inflammatory joint disease (> 6-8 weeks duration) already receiving simple analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) should be considered for referral for specialist rheumatology opinion and DMARD therapy, preferably within 12 weeks.

3.2 MULTIDISCIPLINARY TEAM APPROACH

Effective high quality treatment of early RA is multifaceted and involves the GP, rheumatologist, physiotherapist, occupational therapist, nurse specialist, dietitian, podiatrist, pharmacist and social worker.³⁸ A shared care approach between primary and secondary care physicians,³⁹ facilitated by practice nurses and rheumatology nurse specialists, ensures optimum monitoring of the efficacy and toxicity of drug therapy and the prompt identification of the complications of RA and its treatments.

3.3 PATIENT EDUCATION

A common approach to patient education should be adopted by all members of the multidisciplinary team to ensure that patients receive a consistent health message (see *Annexes 9, 10 and 11*).⁴⁰ Patient education leaflets increase knowledge about the disease.⁴¹ Educational interventions including a psychobehavioural component in addition to providing information appear to have better outcomes in terms of pain relief, joint protection and functional disability, but are labour intensive.^{42, 43}

Patient led self-management education programmes (see *Annex 11 for useful contacts*) are increasing in popularity but evidence of their effectiveness is still limited.^{44, 45} Careful evaluation of these programmes would be required in Scotland if they are to be made available more widely.

- Patient education should be undertaken by all members of the multidisciplinary teams in both primary and secondary care.
- Patients should be provided with an information leaflet/booklet, and if possible, one-to-one education.

3.4 ASSESSMENT OF RESPONSE TO TREATMENT

Quantification of disease activity and outcome is important in assessing, comparing and standardising treatment of RA. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have both devised disease activity

scores which use composite measures so that comparisons can be made between different studies. Both scoring systems are detailed in Annex 5.

Clinical measures of response to treatment include:

- patient opinion (global assessment; see Annex 5)
- physician opinion (global assessment)
- extent of synovitis (number of swollen or tender and both swollen and tender joints)
- duration/severity of stiffness after inactivity
- functional ability (e.g. HAQ score; see Annex 4).

Laboratory measures of response to treatment include:

- acute phase response (ESR, CRP)
- anaemia
- radiological progression.

3.5 HOSPITAL ADMISSION

Selected patients may benefit from more intensive hospital-based treatment from the multidisciplinary team. Most studies comparing inpatient therapy with intensive outpatient therapy have demonstrated the superiority of the former.^{38, 46, 47} One study has compared inpatient with day patient multidisciplinary therapy for patients with uncomplicated active RA and has shown these approaches to be clinically equivalent with little difference in economic costs.⁴⁸ However, a proportion of the costs of day patient treatment are borne by the patient and practical limitations such as travelling time and social circumstances make this option unsuitable for some patients. Thus it is essential that specialist inpatient facilities are maintained for selected RA patients.

3.6 COST OF UNTREATED DISEASE

The costs incurred in delayed treatment of RA are considerable. These include:

- Personal costs
 - lost work opportunities
 - decreased leisure activities
 - stress on relationships
- Costs to society
 - loss of working skills of RA individuals
 - loss of contributions to the home
 - the burden of economic cost for care.

Work disability can occur early in the course of RA, especially in those with manual occupations.^{5,36} Early intervention through retraining and liaison with the patient's employer will help to keep the patient in work for as long as practical and minimise the economic impact of the disease. The most important predictors of work disability are poorer function at the outset, a poorer education level and older age.³ Many patients stop work in the first year after RA onset, highlighting the need for early and effective intervention if work disability is to be avoided.

Overall, patients in the worst functional quartile experience 2.6 times the personal financial cost of those in the best quartile. The hospital costs of the worst quartile are 6.8 times as high. Patients with poor and declining function from the start experience much higher costs of care overall.^{49, 50}

Evidence level 2+

4 Pharmacological management

4.1 ANALGESICS

Analgesics in early RA are used as an adjunct to NSAID and DMARD therapy. There is evidence that paracetamol, coproxamol, nefopam, and codeine are effective in reducing pain in RA.^{51–55} Most of these trials were carried out more than 20 years ago and can be criticised for small patient numbers and short duration. Only a very small proportion of rheumatoid patients is likely to be controlled with analgesics alone.

- Simple analgesics should be used in place of NSAIDs if possible and DMARDs should be introduced early to suppress disease activity.

4.2 NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

There is abundant evidence that NSAIDs are effective and provide symptomatic relief of pain and stiffness without influencing the progression of disease.^{56,57} The choice of short-, medium- or long-acting preparations can be tailored to fit a patient's particular lifestyle.

NSAIDs act by inhibiting cyclooxygenase (Cox) pathways. There are considered to be two isoforms of Cox. Cox1 produces prostaglandins which are cytoprotective and regulatory (GI mucosa, platelets and renal endothelium). Cox2 produces prostaglandins which mediate pain and inflammation and are the preferred targets in RA (see section 4.2.4).

- Prescribers should be aware of the many potential drug interactions with NSAIDs and the side effect profiles of different drugs (see *Annex 6 and the British National Formulary*).⁵⁸

4.2.1 ADVERSE EFFECTS OF NSAIDs

Toxicity is a major limiting factor and side effects are related to dose and duration of therapy.^{59,60} Common side effects (especially in the elderly) are gastrointestinal toxicity, fluid retention and hypertension. Other less common but potentially serious side effects are renal disease and hypersensitivity (including asthma). Uncommon and not usually serious side effects are headaches, dizziness, tinnitus, rash (particularly with fenbufen) and abnormal LFTs (particularly with diclofenac).

Evidence level 1⁺

4.2.2 GASTROINTESTINAL TOXICITY

The use of NSAIDs is associated with gastrointestinal (GI) toxicity.^{59,60} The following side effects occur to a varying extent with all preparations and all routes of administration:

- dyspepsia
- gastric erosions
- peptic ulceration
- small bowel inflammation and bleeding⁶¹
- perforation
- haematemesis or melaena
- occult GI blood loss and anaemia

According to the Arthritis, Rheumatism and Aging Medical Information System (ARAMIS), 13 of every 1000 RA patients who take NSAIDs for one year have a serious gastrointestinal complication. The annual relative risk of mortality attributed to NSAID-related GI adverse effects is four times that for those not using NSAIDs.⁵⁹

The rate of NSAID-related serious GI complications requiring hospitalisation has decreased in recent years. The reason for this is likely to be multifactorial. Intensive education programmes have alerted physicians and patients to the use of newer, less toxic NSAIDs and non-NSAID analgesics in populations at high risk. There has also been a much wider use of gastro-protective therapy.

Risk factors for NSAID-associated gastroduodenal ulcers are listed in Table 4.

Table 4

RISK FACTORS FOR NSAID ASSOCIATED GASTRODUODENAL ULCERS

Definite risk factors	Possible lifestyle factors
Advanced age (<i>linear increase in risk</i>)	Cigarette smoking
History of ulcer	Alcohol consumption
Higher doses of NSAIDs	
Combination use of NSAIDs	
Concomitant use of corticosteroids	
Co-morbidity	

Note: Concomitant administration of anticoagulants will increase the risk of GI haemorrhage.

Some patients who have serious GI complications do not report antecedent dyspepsia. Thus every possible strategy should be employed to minimise risks of GI-related toxicity,⁵⁹ e.g. smoking cessation, and alcohol reduction. Eradication of *Helicobacter pylori* in NSAID-associated peptic ulcers has not been shown to be of value (see the SIGN Guideline on *Helicobacter pylori*: eradication in dyspeptic disease, which is currently under review).⁶²

Surveillance and endoscopic studies have confirmed that the incidence of GI mucosal injury is reduced with nabumetone, etodolac and meloxicam. Mefenamic acid, azapropazone and piroxicam are considered unacceptably toxic for long-term use in RA.^{63, 64}

If NSAID use is unavoidable, gastroprotective agents may be used, as summarised in Table 5.

Table 5

SUMMARY OF GASTROPROTECTIVE AGENTS IN RA

Proton pump inhibitors (PPIs) ⁶⁵	<i>most effective</i>
Prostaglandin analogues ⁶⁶	<i>effective, but less well tolerated compared to PPIs and a problem in premenopausal women</i>
Histamine H ₂ receptor antagonists	<i>less effective than PPIs</i>
Mucosal protective agents (e.g. sucralfate)	<i>less effective than PPIs</i>

It is important to note that the use of an enteric coated, parenteral or rectal NSAID preparation is not protective. The systemic effects of NSAIDs are the predominant cause of damage.

4.2.3 RENAL TOXICITY

NSAID use is also associated with renal disease. Prostaglandins regulate and maintain intrarenal perfusion particularly under conditions where renal blood flow may be reduced (e.g. dehydration or blood loss, cardiac failure, chronic renal failure, diuretic use, or hypertension). By inhibiting prostaglandin synthesis under these conditions, NSAIDs may further impair intrarenal blood flow contributing to renal impairment (or overt renal failure), hyperkalaemia, oedema and hypertension. These problems are particularly likely in the elderly.

Interstitial nephritis is an uncommon, idiosyncratic side effect, unrelated to the above pharmacological action of NSAIDs.

No currently available NSAID has a completely safe renal profile. The effects of the new Cox2 agents (see section 4.2.4) on renal profile are as yet unknown. Preliminary work suggests that the effects of Cox2-selective NSAIDs on renal function are similar to those observed with non-selective NSAIDs.⁶⁷

4.2.4 NEWER NSAIDS

Recent developments have concentrated on Cox pathways. Cox2-selective NSAIDs target the inhibition of inflammatory pathways while having less effect on cytoprotection and regulatory effects than Cox1. Endoscopic ulceration is no more than for placebo with celecoxib.⁶⁸ A recent comparative study of the Cox2-selective NSAID, celecoxib, compared with diclofenac in RA suggested equivalent efficacy with lower frequency of GI ulceration.⁶⁹ Similar findings with regard to upper GI tract were noted with celecoxib in comparison with naproxen⁷⁰ and ibuprofen and diclofenac.⁷¹ The incidence of upper GI complication with rofecoxib (at present unlicensed for RA) has also been shown to be less than that with naproxen.⁷² In this study, both drugs exhibited similar efficacy.

As with all new drugs, the safety of Cox2 inhibitors remains under close review.^{73,74}

4.2.5 SUMMARY OF STRATEGIES TO MINIMISE THE RISK OF NSAID TOXICITY

B The lowest NSAID dose compatible with symptom relief should be prescribed. NSAIDs should be reduced and if possible withdrawn when a good response to DMARDs is achieved.

Simple analgesics should be used in place of NSAIDs if possible and DMARDs should be introduced early to suppress disease activity.

Only one NSAID should be prescribed at a time.

B Introduce gastro-protection in RA patients > 65 years and in those with a past history of peptic ulcer.

Consider intra-articular steroids, particularly when disease is localised (see section 4.5).

NSAIDs should be avoided in patients taking anticoagulants or corticosteroids.

4.3 DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)

DMARDs are drugs which have a beneficial effect on the course of RA, as well as providing symptomatic benefit. Onset of benefit is slow (four to 16 weeks). The currently available agents, associated adverse effects, and their monitoring requirements are indicated in Table 6. Patients should be informed of the potential benefits, risks and monitoring requirements of these drugs.

4.3.1 EVALUATION OF DMARDs

Although the majority of the placebo-controlled studies on DMARDs were carried out in the 1960s, '70s and '80s with methodology which would not necessarily achieve the standards expected in the 1990s, studies have clearly shown benefit from existing DMARDs.^{75–82} The Felson meta-analysis⁷⁵ of 66 trials in 5,343 patients showed a significant improvement in articular index and ESR.

Evidence level I⁺

Further supportive evidence for the use of DMARDs comes from cohort studies where increased disease modifying anti-rheumatic drug use was strongly correlated with better long-term disability index values.⁸³

Evidence level I⁺

There is clear evidence from placebo controlled trials that DMARDs reduce symptoms in RA (as measured by joint pain, swelling, and tenderness, and duration and severity of morning stiffness). DMARDs also improve global wellbeing as assessed by both patient and physician.^{81, 83–88}

Inflammatory markers such as ESR, CRP and elevated platelet count are reduced significantly by DMARDs (but not by NSAIDs) and this is associated with better long-term outcome.^{21, 81, 83–87} An improvement in anaemia of chronic disease is often observed. There is also consistent evidence that DMARDs have a beneficial effect on functional status, as measured, for example, by HAQ score.^{83, 85, 86, 89} Most DMARDs have been shown to have some effect in retarding radiological progression of disease.^{85, 90, 91}

4.3.2 COMPARISON OF DMARDs

The best DMARDs for the treatment of RA are those that provide the most efficacy with the least toxicity over the long term.

Data are available from Fries *et al* and the large ARAMIS database, from the Felson meta-analyses and from direct comparative studies.^{60, 75, 78, 81, 83, 85, 87, 91–96} The range of well-established DMARDs and a brief summary of the advantages and adverse events associated with each is illustrated in Table 6. Recommendations on the choice of DMARD are made in section 4.3.8.

Evidence level I⁺⁺

4.3.3 TIMING OF DMARD TREATMENT IN RA

It is becoming increasingly clear that DMARDs should be introduced as soon as possible. Four recent studies have highlighted the importance of early intervention with DMARDs.^{81, 86–88} Protracted benefit may be achieved in RA patients if appropriate DMARD therapy is introduced early.

Evidence level I⁺

While longer disease duration prior to initiation of DMARDs does not influence the beneficial effect on symptoms or the acute phase response it does have an adverse effect on functional outcome. There is also evidence that delays in initiating DMARDs lead to long lasting negative effects on disease course.^{81, 88} There is clear evidence that patients with early disease respond better to treatment.⁸¹

B Early DMARD therapy in RA is important to maintain function and reduce later disability.

4.3.4 SUSTAINED DMARD THERAPY

While early initiation of therapy is of importance, a sustained input is vital if disease suppression is to be maintained. Remission (see Annex 3) is the goal but is seldom achieved. Equally 'cure' is not attained, thus withdrawal of treatment is seldom appropriate.

Two randomised placebo controlled studies have demonstrated relapse on withdrawal of disease modifying agents.^{97, 98} In both these studies, disease modifying effect was unequivocal. These results confirm the efficacy of DMARDs in comparison with placebo, and demonstrate that sustained prescription of DMARDs is necessary to suppress disease activity. Serial use of DMARDs has been shown to be safe after 10-15 years.^{37, 99}

Evidence level I⁺

B DMARD therapy should be sustained in inflammatory disease in order to maintain disease suppression.

4.3.5 LATE HARM

Uncontrolled disease activity can cause late harm to the patient and this must be weighed against concerns about cumulative or late toxicity when selecting the most appropriate DMARD.¹⁰⁰

Although evidence relating to late harm is patchy and incomplete, the development of malignancies in patients treated with immunosuppressive drugs has been studied.¹⁰¹⁻¹⁰³ In patients who had developed either neoplasms of the immune system or skin or bladder cancer, the adjusted incidence rate ratio for those in the highest cumulative exposure group was 3.7 compared with those in the lowest exposure group.¹⁰³

4.3.6 EFFICACY OF DMARDs

Meta-analysis suggests similar efficacy of sulphasalazine, IM gold, penicillamine and methotrexate.⁷⁵ Double-blind RCTs show equal efficacy of sulphasalazine and methotrexate. Drugs of reduced efficacy from open RCTs include hydroxychloroquine and auranofin.^{80, 92, 93}

Evidence level I⁺

Recent studies suggest sulphasalazine,⁸⁵ methotrexate⁹⁶ and leflunomide have comparable efficacy (details of ACR 20 and ACR 50 are shown in Annex 7). There are no data from adequate studies with respect to azathioprine.

A beneficial effect on radiological progression of RA has been shown with all DMARDs except hydroxychloroquine (which has been shown to have less effect than sulphasalazine in at least one RCT).⁹³

DMARD choice should take into account patient preference and existing co-morbidity.

B Sulphasalazine, methotrexate, IM gold, and penicillamine are equally effective DMARDs.

4.3.7 TOXICITY OF DMARDs

Toxicity assessment in the initial Felson meta-analysis came from 71 clinical trials that contained 129 treatment groups.⁷⁵ Over one year almost one third of the patients (30.3%) stopped therapy. Half of these did so because of drug toxicity. In this meta-analysis injectable gold had higher toxicity rates and higher total dropout rates than the other drugs. Antimalarials and auranofin had relatively low rates of toxicity. In a subsequent meta-analysis the same authors updated their previous meta-analyses by adding trials published through 1990 and trials of azathioprine.⁷⁶ Antimalarial drugs

Table 6: DMARD PROFILES

Established DMARDs	Common/minor adverse events	Rare/severe adverse events	Monitoring requirements	Advantages of this drug
Hydroxychloroquine ^{78, 80, 104, 105, 116, 118}	Nausea, headaches	Retinal toxicity	Eye check* Reduce dose if renal impairment	No blood monitoring required Can use when uncertain of diagnosis (e.g. inflammatory arthritis, connective tissue disease) Can use despite leucopenia or thrombocytopenia
Sulphasalazine ^{85, 92, 106-108}	Nausea, diarrhoea, headache Mouth ulcers, rash, Oligospermia (reversible) Staining of soft contact lenses Abnormal LFTs	Leucopenia	FBC Liver and renal function Urinalysis	Rapid onset action (8-12 weeks) Can use when uncertain of diagnosis (e.g. reactive/ psoriatic/ RA) Relatively safe in thrombocytopenia
Methotrexate ^{**94, 96, 109, 110, 111, 114}	Nausea, diarrhoea Mouth ulcers, rash Alopecia Abnormal LFTs	Leucopenia/ Thrombocytopenia Pneumonitis Sepsis Liver disease (late) Nodulosis Epstein-Barr virus associated-lymphoma	FBC Liver and renal function Advise to restrict alcohol intake	Rapid onset action (6–10 weeks) Can use when uncertain of diagnosis (e.g. RA, psoriatic/ connective tissue disease) Can be given orally, IM or SC Weekly administration
IM gold ^{80, 81, 94}	Mouth ulcers, rash Nitritoid reactions***	Thrombocytopenia/ Leucopenia Proteinuria Colitis	FBC Liver and renal function Urinalysis	Patient preference Ensures compliance
Penicillamine ^{80, 112}	Nausea/loss of taste Dose related, reversible fall in platelet count	Proteinuria Late autoimmune disease	FBC U&E Urinalysis	
Auranofin ^{84, 92}	Diarrhoea	Leucopenia	FBC Renal function Urinalysis	Oral gold option
Azathioprine ¹¹³	Nausea	Leucopenia Sepsis Lymphoma (late) ¹⁰³	FBC Liver function	Can use in patients with renal disease
Leflunomide ^{85, 96, 114}	Alopecia Diarrhoea Nausea Rash	Leucopenia Hepatitis Thrombocytopenia	FBC Liver and renal function BP monitoring	Remain to be established (<i>recently introduced</i>)
Cyclosporin ¹¹⁵	Paraesthesia/tremor/ headaches Hypertrichosis Gingival hypertrophy Nausea	Hypertension Renal disease Sepsis	Liver and renal function BP monitoring	

* see ophthalmology¹¹⁶ and BSR guidelines¹¹⁷ (see Annex 11 for website addresses) and relevant datasheets¹¹⁸

** supplement with folic acid¹²³

*** vasomotor symptoms post-injection – a feature seen early in treatment which usually resolves if treatment is continued

Other DMARDs

Minocycline ¹¹⁹⁻¹²²	Although three recent RCTs have shown an effect of minocycline compared with placebo at present it is not licensed for treatment of RA. Dizziness and skin pigmentation are common side effects.
--------------------------------	--

had the lowest toxicity rate of all those studied, but efficacy was only moderate. Methotrexate had the most favourable efficacy/toxicity trade off. Sulphasalazine scored close to methotrexate but in that meta-analysis was slightly more toxic.

A meta-analysis of RCTs of folic or folinic acid supplementation during low dose methotrexate therapy for RA showed that 5 mg folic acid weekly is useful in reducing mucosal and gastrointestinal side effects.^{110,123}

4.3.8 CHOICE OF DMARD

Overall there is consistent evidence that hydroxychloroquine and auranofin^{75,76,92,93} are relatively weak DMARDs with a slower onset of action, while intramuscular gold, penicillamine, sulphasalazine⁹² and methotrexate^{75,76} have very comparable clinical effects on disease activity. More patients are likely to continue on sulphasalazine (and with better effect) compared to auranofin and on methotrexate compared with other DMARDs.

B Sulphasalazine and methotrexate are the current DMARDs of choice due to their more favourable efficacy/toxicity profiles.

Successive DMARDs are required for most patients in the medium to long term.¹²⁴

4.3.9 PRACTICAL PRESCRIBING OF DMARDs

- Patients should be counselled about the benefits and risks of specific DMARDs, and should be provided with additional written information.
- Good liaison between primary and secondary care is essential. Rheumatology nurse specialists have an important role in this aspect of care.
- Monitor for continued efficacy (ESR/CRP, number of tender and swollen joints, duration of morning stiffness, function).
- Monitor toxicity using British Society of Rheumatology/local guidelines or manufacturers' data sheet recommendations.
- Clear advice about the monitoring of specific DMARDs should be available to the patient, GP and practice nurse.

4.3.10 COMBINATION DMARD THERAPY

Combination DMARD therapy in RA is being increasingly used by rheumatologists, but evidence of benefit remains patchy.

A meta-analysis in 1994 concluded that combination therapy does not offer a substantial improvement in efficacy,¹²⁵ whilst toxicity was increased.

Evidence level I⁺

Since the 1994 Felson meta-analysis¹²⁵ there have been six parallel (five blind,^{126–130} one open¹³¹), five step-up^{132–136} (two using biological agents^{128,135}) and one step-down, combination DMARD¹³⁷ studies. Overall the results have been disappointing.

The addition of cyclosporin to methotrexate in patients with established RA has been shown to be of benefit, but it is not known if the same effect could have been achieved by changing to cyclosporin alone.¹³³ Benefit of a combination of methotrexate, sulphasalazine and hydroxychloroquine has been shown but was not studied in early disease.¹²⁸ A recent controlled study of iv infliximab in patients with partial response to methotrexate provided additional clinical benefit and prevented further radiological damage. However, the study was conducted in patients with longer disease duration than applies to the patients covered by this guideline.¹³⁶

Evidence level I⁺

One study used very high doses of prednisolone (60 mg daily initially) which could not be sustained for prolonged periods in clinical practice without unacceptable cumulative toxicity.¹³⁷

A recent open combination study using a variety of DMARDs showed significantly more patients in remission in the combination group and adverse events were of similar frequency. However, the mean improvement in symptoms, clinical signs and function were similar across the groups making this analysis difficult to interpret.¹³¹

Evidence level I⁻

In the treatment of poor prognosis early RA, the combination of methotrexate, cyclosporin and targeted intra-articular steroid did not have significant advantages over monotherapy with sulphasalazine in terms of joint damage and function after one year.¹³⁸

Benefit was seen with the addition of etanercept to methotrexate in RA patients with long disease duration and infliximab to methotrexate but at present there is no confirmatory evidence in patients with early disease.^{134, 135}

B At present the balance of evidence does not support the routine use of combination DMARD therapy in early RA.

4.4 TARGETED IMMUNOTHERAPY

Tumour necrosis factor (TNF) is a product of macrophages which acts on the immune system to induce the production of powerful pro-inflammatory mediators. TNF is thus a potential molecular target for the treatment of RA. Two agents with anti-TNF activity have recently become available for RA patients:

1. Infliximab – a chimeric monoclonal antibody which is given as an intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks. Side effects include mild infusion reactions and development of antibodies. Infliximab has been used with methotrexate in part to suppress antibodies against the drug. Results from a double-blind study as an addition to methotrexate have shown encompassing ACR 20 and 50 responses. There was also one death during the period of the study.¹³⁴
2. Etanercept is a TNF receptor fusion protein designed to bind circulatory TNF. It can be administered alone or with methotrexate. It is given as twice weekly subcutaneous injection. Results from placebo-controlled studies are shown in Annex 7. Although no major complications were seen in clinical trials, serious and fatal infections have occurred post-marketing in the USA. A recent double-blind study comparing two doses of etanercept with methotrexate has shown significant advantage of 25 mg etanercept twice weekly in terms of ACR 20, 50 and 70 outcomes and erosion scores. There were also fewer infections in the patients taking etanercept.¹³⁹

There are concerns that continued inhibition of pro-inflammatory molecules may increase the risk of infection and cancer, particularly lympho-proliferative malignancies. Evidence in this respect is still awaited. The exact role of TNF blockade in early disease has yet to be elucidated and their greater costs may preclude widespread early use.

4.5 INTRA-ARTICULAR CORTICOSTEROIDS

Intra-articular corticosteroid injections are widely used to provide rapid, and sometimes sustained, symptomatic relief in 'target' joints.

Intra-articular corticosteroid injections:

- allow local treatment of inflamed joints whilst minimising undesirable systemic effects

- provide symptomatic relief pending the onset of DMARD effect
- treat particularly troublesome joints where the overall disease control is good
- deal with mono/oligo arthritis in instances when DMARDs are deemed inappropriate.

However, there are few controlled trials in this area and no evidence on the long-term effect on disability or radiological progression. Experience from large cohorts suggests that complications such as joint sepsis are very rare.¹⁴⁰ Synovial fluid aspiration at time of joint injection has been shown to reduce relapse rate.¹⁴¹

Post-injection rest (24 hours) has shown enhanced improvement in symptomatic relief. Walking times were also improved by this approach.¹⁴²

4.5.1 PRACTICAL PRESCRIBING OF INTRA-ARTICULAR CORTICOSTEROIDS

- Intra-articular injections can be used for rapid, and sometimes sustained, symptomatic relief in 'target' joints.
- Intra-articular injections to any one joint should not be given more than three times in one year.
- When administering intra-articular injections:
 - use sterile technique
 - advise patients how to seek help if joint fails to settle after injection
 - always consider possible septic arthritis in differential diagnosis of mono/oligo flare in RA.

4.6 SYSTEMIC CORTICOSTEROIDS – ORAL AND PARENTERAL

4.6.1 SYMPTOMATIC BENEFIT

The symptom relieving anti-inflammatory effects of corticosteroids are well established.¹⁴³ Recent randomised controlled studies have shown that this benefit is not sustained beyond nine months when either continuous low-dose corticosteroids (7.5 mg/day)¹⁴⁴ or high-dose 'step-down' therapy,¹³⁷ is given as an adjunct to DMARDs or NSAIDs.

Evidence level 2+

Bridge corticosteroids (usually IM) are an option to provide symptomatic relief until DMARDs become effective. These show benefit in some patients but their value is limited by possible 'rebound' flare of symptoms on discontinuation.¹⁴³

4.6.2 ACUTE PHASE RESPONSE

In many trials the effect of corticosteroids has been obscured by the concurrent use of other treatments known to affect the acute phase response. No additional benefit of corticosteroid compared to placebo was seen with low-dose steroid study,¹⁴⁴ but a significantly more rapid fall in the ESR was apparent with the higher doses used by Boers.¹³⁷ The effect on acute phase response had disappeared by one year (by which time the corticosteroid had been discontinued).

4.6.3 FUNCTIONAL RESPONSE

Although some benefit in function from corticosteroids was reported,¹⁴⁵ no objective long term benefit was discerned. Recent studies using the well-validated health assessment questionnaire (HAQ)¹⁷ to measure function have

shown an early advantage of high-dose 'step-down' corticosteroids.¹³⁷ However, the improved HAQ scores seen with adjunctive continuous low-dose steroid were no longer significant by one year and disappeared beyond 15 months.¹⁴⁴ To date, no controlled study of systemic corticosteroid has truly addressed the important assessment of disability as a long term outcome.

4.6.4 RADIOLOGICAL PROGRESSION

A number of early studies suggested that oral corticosteroids may inhibit radiological damage and recent randomised controlled trials confirm this finding.^{137,144}

The development of new erosions was reduced by 23% and the progression of existing damage was highly significantly retarded on hand x-rays of patients taking low-dose corticosteroid for two years.¹⁴⁴ On discontinuing corticosteroid therapy radiological progression was again seen at pre-treatment rate.¹⁴⁶

Evidence level 1⁺

A high dose step-down regimen of corticosteroid with combination DMARD also demonstrated inhibition of erosions but had no effect on joint narrowing.¹³⁷

It should be noted that a significant proportion of placebo treated patients in both studies did not develop erosions during the study.^{137,144}

4.6.5 CUMULATIVE TOXICITY

Osteoporosis was not formally measured in the Kirwan trial of continuous low-dose oral corticosteroid.¹⁴⁴ In a cohort study of 8,068 patients given a mean dose of 5 mg of prednisolone per day, both reduced bone mineral density and increased fractures were demonstrated over four years. A relative fracture risk of 2:1 was derived for corticosteroid use after correction for multiple variables.¹⁴⁸

Evidence level 2⁺

Two case control studies show increased adverse events in corticosteroid treated rheumatoid arthritis patients, including cataracts, infections (the Committee on Safety of Medicines has drawn attention to the risks of chicken pox exposure in patients not previously infected¹⁴⁸), gastrointestinal bleeds, avascular necrosis and fractures.¹⁴⁹⁻¹⁵¹ Increased mortality has also been reported.¹⁵² There is the possibility that corticosteroid treated patients may have had more severe disease.

Both cumulative and average steroid doses are independent, important adverse event predictors.¹⁵¹ Longer term studies are required to identify the cumulative long-term effect from continuous low-dose corticosteroid and from step-down or intermittent regimens.

Most clinicians withdraw oral corticosteroids slowly (e.g. 1 mg/month when below 15 mg daily) to avoid rebound flare of symptoms.

4.6.6 PRACTICAL PRESCRIBING OF SYSTEMIC CORTICOSTEROIDS

The short term symptomatic benefit of systemic corticosteroids and the apparent prevention of radiological damage must be weighed against the risk of significant morbidity. Until additional, adequately powered and long term studies are performed to address the benefits and risks the *routine* use of oral corticosteroids cannot be recommended. In specific situations where there are strong contraindications to NSAID prescription, or difficulties in using DMARDs, systemic corticosteroids may be acceptable.

B Oral corticosteroids are not recommended for routine use, as there is no sustained clinical or functional benefit and there is high risk of toxicity with long term use.

- Inform patients of the risks of corticosteroids prior to prescription and issue a steroid warning card.
- Intramuscular corticosteroid allows control of dose and duration of therapy and may be preferable to oral therapy.
- Oral corticosteroids should be withdrawn slowly to avoid rebound flare of symptoms.

D The lowest possible dose of corticosteroid should be used for the shortest possible time.

D Monitor patients closely for adverse corticosteroid effects. Be alert to the possibility of diabetes, cataract and infection. Inform patients not previously infected of the danger of chicken pox/shingles exposure.

- Ensure adequate prophylaxis and treatment of osteoporosis in patients taking oral corticosteroids.

4.7 COMPLEMENTARY MEDICINE

Few studies in this field relate specifically to rheumatoid arthritis and many studies have been excluded from the guideline on the grounds of small numbers and poor design.

There is unsatisfactory evidence of possible subjective benefit of homeopathy over placebo.^{153–155} A proprietary remedy 'Rheumalex' appeared to help in pain relief, but the herbal substance feverfew showed no evidence of benefit.^{156,157} Acupuncture showed no benefit in one meta-analysis reviewed but the quality of this analysis was limited.^{158,159} There is no evidence that Seatone or selenium produced any clinical benefit.^{160–162}

While no evidence of effectiveness is not the same as evidence of ineffectiveness the lack of adequate research studies precludes firm conclusions. Patients have a perception that because these treatments are 'natural' they are without side effects but this is not the case.¹⁶³

Further research is clearly needed and should include close monitoring of possible harm as well as potential benefit.

4.8 OTHER THERAPIES

4.8.1 HORMONE REPLACEMENT THERAPY

Although RA patients on hormone replacement therapy (HRT) have been shown to report a significant increase in general wellbeing compared with placebo, there is to date no evidence of alteration in indices of disease activity.^{164,165} HRT is of undoubted benefit in improving bone mineral density in postmenopausal women with RA and associated osteoporosis.¹⁶⁶

4.8.2 IRON THERAPY

Anaemia is common in RA and is not always due to iron deficiency. Unnecessary iron supplements should be avoided. Patients who are truly iron deficient should be assessed and any dietary deficiency should be corrected. GI blood loss requires investigation and specific therapy e.g. proton pump inhibitor (see *section 4.2.2*). Ferritin acts as an acute phase reactant in RA, thus a 'normal' ferritin does not exclude iron deficiency.

5 The role of the multidisciplinary team

- ☑ The multidisciplinary team has been shown to be effective in optimising management of patients with RA.³⁸ All patients should have access to a range of health professionals, including general practitioner, rheumatologist, nurse specialist, physiotherapist, occupational therapist, dietitian, podiatrist, pharmacist and social worker.

5.1 OCCUPATIONAL THERAPY

In everyday practice, the substantial impact of skilled occupational therapy (OT) intervention on quality of life for patients with RA is clear. Unfortunately, relatively few studies have been carried out and evidence from RCTs is often lacking. The OT approach is multifaceted and includes:

5.1.1 ACTIVITIES OF DAILY LIVING

Facilitation of the activities of daily living (e.g. washing, toileting, dressing, cooking, eating, working), sometimes with the provision of equipment and adaptations, is fundamental to the management of RA.¹⁶⁷ Effective OT advice is crucial in helping patients to maximise function and improve their level of independence.

Evidence level 1⁺

- C **Skilled occupational therapy advice should be available to those experiencing limitations in function.**

5.1.2 JOINT PROTECTION

Joint protection aims to reduce pain and stress on joints whilst carrying out everyday activities.¹⁶⁸

Evidence level 4

A range of strategies are employed including adapting movement patterns of affected joints to reduce strain, assistive devices, rest regimens, energy conservation techniques, exercise and splinting. These interventions are difficult to evaluate and formal studies are limited. Studies in patients with longer disease duration, have shown encouraging results.

5.2 PHYSIOTHERAPY

The role of the physiotherapist in assessing and treating patients with RA is well recognised in clinical practice. Physiotherapy management has been shown to be effective in improving self-efficacy, knowledge and morning stiffness.¹⁶⁹ However, well-conducted studies evaluating the effectiveness of intervention are lacking and the formal evidence base is limited.

5.2.1 DYNAMIC EXERCISE THERAPY

Exercise therapy is prescribed in an attempt to overcome the adverse effects of RA on muscle strength, endurance and aerobic capacity. Dynamic exercise therapy (i.e. exercises of low to moderate aerobic intensity) is effective in increasing aerobic capacity and muscle strength. No adverse effects on disease activity or pain are observed.¹⁷⁰ Limited evidence indicates that specific strength training programmes can reduce impairment.¹⁷¹

Evidence level 1⁺⁺

- B **Patients should be encouraged to undertake simple dynamic exercises.**

5.2.2 HYDROTHERAPY

Hydrotherapy is one of the oldest forms of treatment for patients with arthritis. Despite this, formal evidence showing benefit is sparse. Limited evidence suggests that hydrotherapy can effect and maintain an improvement in self-efficacy in addition to some clinical and psychological gain.^{172, 173} A recent systematic review of balneotherapy¹⁷⁴ (i.e. hydrotherapy or spa therapy) noted that no conclusion could be provided from the reviewed studies due to poor methodology. Further well-conducted trials are needed to assess the efficacy of this mode of treatment.

5.2.3 OTHER PHYSICAL THERAPIES

Evidence for other therapies such as the application of ice or heat,¹⁷⁵ TENS or laser therapy^{176–179} is conflicting or is insufficient to support their routine use. There is limited evidence showing symptomatic benefit from ultrasound.¹⁸⁰

5.3 SPLINTING

Splinting can be undertaken by occupational therapists, physiotherapists, or orthotists. Good evidence to support the use of resting hand splinting is sparse although two studies did report a significant reduction in pain when splints were applied.^{181,182} Wrist working splints have been shown to decrease pain on activity^{183,184} but do not improve function, grip strength or dexterity.^{185,186} There is no good evidence to support the use of splints to correct ulnar deviation or any other deformity.

Evidence level I⁺

C Resting and working splints can be used to provide pain relief.

5.4 PODIATRY

The importance of appropriate footwear provision for comfort, mobility and stability is well recognised in clinical practice but there is little evidence-based research to support such observations in patients with early RA.

There is some evidence regarding the efficacy of foot orthoses in terms of both comfort level and stride speed and length.^{187–189}

The guideline development group could find no research regarding other podiatry interventions such as reduction of callosities and padding of the feet in those with early RA.

Podiatry referral should be offered to all patients.

5.5 DIETETICS

Nutritional advice plays an important part in the management of a patient with RA. Enquiries about diet are amongst those most commonly received from patients.

5.5.1 WEIGHT MANAGEMENT

Weight reduction in obese individuals is important particularly when weight bearing joints are involved. Management should be as recommended in the SIGN guideline on obesity.¹⁹⁰

Cachexia may occur in those with severe active RA. The aetiology is likely to be multifactorial. Several studies have shown that patients with low body mass index (BMI) do less well and have poorer functional status.^{191,192} Whilst it is not clear whether dietary intervention improves outcome, for general health reasons, an adequate BMI should be maintained. Some patients will require diet supplements in addition to dietary advice.

5.5.2 DIET AS THERAPY

Relatively few studies have been carried out to assess the effect of diet therapy on disease activity in RA.¹⁹³ Fasting has been shown to be of benefit in some patients.¹⁹⁴ Weight loss often occurs and this may not be beneficial in all patients. Practical difficulties have also been encountered in implementing and maintaining strict dietary changes. The evidence regarding food exclusion is often anecdotal and is inconclusive. Exclusion/elimination diets can be difficult to follow and if adhered to over a long period of time, may lead to the development of nutritional deficiencies.

5.5.3 DIET SUPPLEMENTS

A meta-analysis of clinical trials of fish oil supplementation in RA concluded that there was a significant reduction in the number of tender joints and in duration of morning stiffness after three months of therapy. However, no effect was seen on indices of disease activity or progression of RA.¹⁹⁵ There are practical limitations to this approach, including the large quantities of fish oil required. The latter is expensive, difficult to take and not available on prescription.

The effect of other oils such as evening primrose oil¹⁹⁶ and blackcurrant seed oil¹⁹⁷ on disease activity in RA remains uncertain.

Annex 1

DETAILS OF SYSTEMATIC REVIEW UNDERTAKEN FOR THE GUIDELINE

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by the SIGN Information Officer in collaboration with members of the guideline development group.

Searches were restricted to systematic reviews, meta-analyses, randomised controlled trials, and longitudinal studies. Inclusion criteria were patients with rheumatoid arthritis within five years of diagnosis, aged over 16. Exclusion criteria were studies based outside Western Europe, Scandinavia, North America, Australia or New Zealand; surgery; psychological treatments; social care or social support of patients.

Searches were carried out on the Cochrane Library, Embase, Medline, and Pascal from 1985 onwards. A subsearch on alternative or traditional therapies also looked at the Allied & Alternative Medicine and Mantis databases. All search strategies were evaluated by an independent information specialist.

The main searches were supplemented by material identified by individual members of the development group. All selected papers were evaluated using standard methodological checklists before conclusions were considered as evidence.

The question of late harm caused particular difficulties in searching. The section of the strategy on this topic focused on the long-term toxicity or toleration of DMARDs. It is recognised that this limited approach does not fully cover the literature on this subject, but given the restricted time available to complete the development process it was decided to accept this limitation.

Annex 2

AMERICAN RHEUMATISM ASSOCIATION 1987 REVISED CRITERIA FOR THE CLASSIFICATION OF RHEUMATOID ARTHRITIS¹⁶

Diagnosis of rheumatoid arthritis requires four of seven of the following criteria. In criteria one to four the joint signs or symptoms must be continuous for at least six weeks.

Signs & Symptoms	
1. Morning stiffness	Duration > 1hr lasting > 6 weeks
2. Arthritis of 3 or more joint areas*	Soft tissue swelling or effusion lasting > 6 weeks
3. Arthritis of hand joints	Wrist, metacarpophalangeal joints or proximal interphalangeal joints lasting > 6weeks
4. Symmetric arthritis*	At least one area, lasting > 6 weeks
5. Rheumatoid nodules	As observed by a physician
6. Serum rheumatoid factor	As assessed by a method positive in less than 5% of control subjects
7. Radiographic changes	As seen on anteroposterior films of wrists and hands

* Possible areas: proximal interphalangeal joints, metacarpophalangeal joints, wrist, elbow, knee, ankle, metatarsophalangeal joints (observed by a physician).

At least four criteria must be fulfilled.

Annex 3

CRITERIA FOR COMPLETE REMISSION IN RA

Complete remission is achieved with five of the following six:

1. morning stiffness < 15 minutes
2. no fatigue
3. no joint pain (history)
4. no joint tenderness or pain on motion
5. no soft tissue swelling in joint/tendon sheaths
6. Westergren ESR < 30mm/hr (F) < 20mm/hr (M)

Exclusion: extra-articular disease

Annex 4

HEALTH ASSESSMENT QUESTIONNAIRE¹⁷

Patient Label		Date		
<p>We are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments at the end of this form.</p> <p>PLEASE TICK ONE RESPONSE WHICH BEST DESCRIBES YOUR USUAL ABILITIES OVER THE PAST WEEK:</p>				
	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	Unable to do
	<i>Score = 0</i>	<i>Score = 1</i>	<i>Score = 2</i>	<i>Score = 3</i>
1. DRESSING AND GROOMING - Are you able to				
Dress yourself, including tying shoelaces and doing buttons?				
Shampoo your hair?				
2. RISING - Are you able to				
Stand up from an armless straight chair?				
Get in and out of bed?				
3. EATING - Are you able to				
Cut your meat?				
Lift a full cup or glass to your mouth?				
Open a new carton of milk (or soap powder)?				
4. WALKING - Are you able to				
Walk outdoors on flat ground?				
Climb up five steps?				
PLEASE TICK AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES:				
Walking stick		Crutches		
Devices for dressing e.g. buttonhook, zipper pull, long handled shoe horn		Special or built-up chair Wheelchair		
Walking frame		Other (please specify)		
Built-up or special utensils				
PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON:				
Dressing and grooming		Rising		Eating
				Walking

HEALTH ASSESSMENT QUESTIONNAIRE *continued*

	Without ANY difficulty <i>Score = 0</i>	With SOME difficulty <i>Score = 1</i>	With MUCH difficulty <i>Score = 2</i>	Unable to do <i>Score = 3</i>
5. HYGIENE - Are you able to				
Wash and dry your entire body?				
Take a bath?				
Get on and off the toilet?				
6. REACH - Are you able to				
Reach and get down a 5lb object (e.g. a bag of potatoes) from above your head?				
Bend down to pick up clothing from the floor?				
7. GRIP - Are you able to				
Open car doors?				
Open jars which have been previously opened?				
Turn taps on and off?				
8. ACTIVITIES - Are you able to				
Run errands and shop?				
Get in and out of a car?				
Do chores such as vacuuming, housework or light gardening?				
PLEASE TICK AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES:				
Raised toilet seat		Jar opener (for jars previously opened)		Long handled appliances for reach
Bath seat		Bath rail		Other (please specify)
PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON:				
Hygiene		Reach		Gripping and opening things
				Errands and housework
SCORING OF HAQ				
Add the maximum score for each of the 8 sections and divide by 8 to give a score between 0–3. If aid/device or help is needed the score for that activity automatically = 2 (unless 3 has already been ticked.)				
Normal function = 0				
Most affected function = 3				

Annex 5

EVALUATION OF DMARD EFFECT

1. ACR IMPROVEMENT CRITERIA¹⁹⁸

- tender joint count*
- swollen joint count*
- at least three of:
 - global disease activity – investigator
 - global disease activity – patient**
 - patient assessment of pain
 - physical disability score, e.g. HAQ
 - acute phase reactant

ACR 20, ACR 50 and ACR 70 indicate 20%, 50% and 70% improvement in the above

* *extent of synovitis is measured by doing a count of number of tender joints and number which are both swollen and tender.*

** *patient opinion of disease activity measured on a 10 cm visual analogue scale. Anchor points at either end of the scale are 'not active at all' and 'extremely active'.*

2. EULAR RESPONSE CRITERIA¹⁹⁹

Disease activity score (DAS) is derived using a nomogram which incorporates the following four measures:

- Ritchie articular index²⁰⁰
- swollen joint count
- ESR (Westergren)
- general health score

DAS > 2.8 is usual level of activity for enrolment in DMARD studies

Interpretation of change in disease activity score from baseline evaluation of response:

- > 1.2 good
- > 0.6 moderate ≤ 1.2
- ≤ 0.6 non-responder

3. RADIOLOGICAL ASSESSMENT

Sharp method²⁰¹ (scores erosions and joint space narrowing)

Larsen method²⁰² (utilises standardised films that illustrate progressive destructive disease)

Annex 6

Awareness of and vigilance for drug interactions is important, but concern about drug interactions should not prevent the prescription of drugs that are needed to reduce joint damage in early RA. Much more morbidity will accrue from leaving RA untreated than will occur as a result of these interactions.

DRUG INTERACTIONS WITH NSAIDs

Drug	Effect of NSAID on drug	Principal mechanism*
Antihypertensives (ACE Inhibitors, Angiotensin II receptor antagonists)	Therapeutic effect decreased Hyperkalaemia and renal impairment increased	Sodium retention Interference with intrarenal prostaglandins
Warfarin	Therapeutic effect increased	Displaced protein binding Inhibition of drug metabolism
Sulphonylureas	Therapeutic effect increased	Displaced protein binding
Cyclosporin	Risk of nephrotoxicity increased	
Methotrexate	Therapeutic effect increased	Reduced renal clearance
Digoxin	Therapeutic effect increased	Reduced renal clearance
Lithium	Therapeutic effect increased	Reduced renal clearance
Phenytoin	Therapeutic effect increased	Displaced protein binding

Risk of GI haemorrhage is increased in patients on warfarin or corticosteroids. Further interactions are listed in the British National Formulary, Appendix 1⁵⁸

** the mechanisms underlying drug interactions are complex*

DRUG INTERACTIONS WITH DMARDs

Drug	Interacts with
Azathioprine	Allopurinol Co-trimoxazole, trimethoprim, rifampicin Possibly warfarin
Hydroxychloroquine	Amiodarone Antiepileptics Digoxin
Cyclosporin	Multiple drugs, grapefruit juice
D-penicillamine	Antacids, zinc, iron (including proprietary indigestion tablets or mixtures) <i>N.B. should not be taken together</i>
Sulphasalazine	Digoxin
Methotrexate	Aspirin/NSAIDs Co-trimoxazole, trimethoprim, phenytoin All antifolate drugs Cyclosporin
Leflunomide	Phenytoin Warfarin Tolbutamide
Minocycline	Other hepatotoxic/haemotoxic drugs Antacids, zinc, iron Cyclosporin

Further interactions are listed in the British National Formulary, Appendix 1⁵⁸

Annex 7

EXTENT OF RESPONSE TO SINGLE AGENTS IN RECENT DMARD STUDIES

Drug	Dose	no. in study	median disease duration	median duration of study	proportion achieving response	
					ACR 20 [†]	ACR 50 [†]
Sulphasalazine ¹³⁰	2-3 g/day	68	1 year	1 year	59%	[34%]*
Sulphasalazine ⁸⁵	2 g/day	133	7 years	0.5 year	44%	30%
Methotrexate ¹³⁰	7.5-15 mg/day	69	1.5 years	1 year	59%	[38%]*
Methotrexate ⁹⁶	7.5-15 mg/day	182	6 years	1 year	35%	23%
Methotrexate ¹³⁹	7.5-20 mg/day	217	1 year	1 year	65%	42%
Leflunomide ⁸⁵	20 mg/day	133	8 years	0.5 year	48%	33%
Leflunomide ⁹⁶	20 mg/day	182	7 years	1 year	41%	34%
Etanercept ¹³⁹	10 mg twice weekly (subcutaneous)	208	1 year	1 year	64%	32%
Etanercept ¹³⁹	25 mg twice weekly (subcutaneous)	207	1 year	1 year	72%	48%

*figures in [] reflect Dougados report of EULAR "good" responders

† see Annex 5

Annex 8

RECOMMENDATIONS FOR FURTHER RESEARCH

The following are suggested as potential areas for further research:

GENERAL

1. The definition of early RA.
2. Clarification of the important factors for diagnosis and prognosis.
3. Inception cohort studies to investigate the combination of prognostic factors that will predict disease severity in individual patients and allow patients suitable for early aggressive therapy to be identified.
4. Evaluation of new imaging techniques to assess early joint damage.
5. Audit of referral time from symptom onset to rheumatology clinic appointment: resource implications of delay before specialist review.

PHARMACOLOGICAL MANAGEMENT

NSAIDs

1. Further evaluation of highly selective Cox2 agents:
 - will they reduce the incidence of ulcer complications in routine clinical practice?
 - will it be necessary for GI protective agents to be co-prescribed in patients at high risk of ulcer complications?
 - what effect will they have on NSAID-associated renal and cardiovascular events?
2. NSAIDs which block nitric oxide synthetase.

DMARDs

1. The optimum treatment strategy for achieving remission in early RA using existing/new DMARDs. This should include:
 - the most appropriate action if a patient fails to achieve an adequate response to methotrexate or sulphasalazine
 - long term, adequately powered studies of the combination of methotrexate and sulphasalazine in early disease
 - prospective study of other combination options
 - assessment of long term safety issues.

CORTICOSTEROIDS

1. Long term, adequately powered studies to investigate whether continuous low-dose prednisolone and step-down prednisolone regimens will reduce joint damage/disability in the long term.
2. Assessment of cumulative toxicity.

TNF BLOCKADE AND NOVEL THERAPIES

1. The role of anti-TNF therapy in the treatment of patients with early RA:
 - as 'bridge therapy' to induce remission while waiting for DMARDs to take effect
 - in combination with DMARD therapy when there has been insufficient beneficial effect
 - as monotherapy in RA
 - the optimal dosage and method of administration of anti-TNF therapy and the issue of immunogenicity

- efficacy of anti-TNF agents in preventing joint damage and maintaining function over the longer term
 - long term data on whether anti-TNF therapy will increase susceptibility to infection or tumours
 - pharmacoeconomic analyses of anti-TNF therapy including indirect costs associated with RA (e.g. disability and unemployment).
2. Evaluation of future possibilities for biological therapy in RA, such as:
 - IL-1 receptor blockade with recombinant human IL-1 receptor antagonist
 - blockade of IL-6 receptors
 - anti-inflammatory cytokines such as IL-10 and IL-4
 - targeting T-cells e.g. anti-CD4 antibodies.
 3. Evaluation of matrix metalloproteinase inhibitors in early RA.

THE ROLE OF THE MULTIDISCIPLINARY TEAM

1. Evaluating early intervention by the multidisciplinary team versus medical care alone and the impact on functional ability.
2. Evaluation of rheumatology nurse specialist role.
3. Physiotherapy
 - compliance with exercise and its relationship to longer term outcome
 - the effect of exercise training programmes on muscle strength and function
 - inpatient versus outpatient physiotherapy in the management of early RA.
4. Occupational therapy
 - efficacy of joint protection techniques.
5. Splinting
 - short and longer term evaluation of resting and working splints.
6. Podiatry
 - effect of foot orthoses on foot deformity and pain.
7. Dietetics
 - RCTs of dietary supplements such as antioxidants
 - further research on the possible drug-sparing effect of fish oils.
8. Pharmacy
 - the role of the pharmacist in patient education about drug therapy
 - the pharmacist's role in monitoring for drug interaction and side effects.

PATIENT INVOLVEMENT

1. The emotional impact of being diagnosed with RA and the value of psychological input.
2. Assessment of patient attitudes to early aggressive treatment.
3. Strategies to try to maintain patient employment: vocational assessment and retraining if necessary.
4. RCTs of educational interventions including patient led self-management courses in early RA (evaluating their impact on disability and emotional distress).
5. RCTs of psychological therapy such as cognitive behavioural therapy in early RA (evaluating their impact on disability and emotional distress).

OTHER ASPECTS

1. RCTs of complementary therapies in early RA evaluating benefit and harm.
2. Homeopathy in early RA.

Annex 9

KEY MESSAGES FOR PATIENTS

These key messages are not intended for direct dissemination to patients, but are provided for possible use by clinicians in discussing treatment options with patients who have RA. They may be incorporated into local patient information materials, an example of which is shown in Annex 10.

- In RA joints become inflamed making them painful, swollen and stiff.
- The cause of RA is unknown.
- There is no single test to diagnose RA.
- RA cannot be cured at present, but in many cases it can be controlled.
- The progression of RA is different in each person.
- RA can be treated; reducing pain, stiffness, swelling and damage to joints.
- The sooner RA is treated the better, the earlier treatment is started the less damage takes place in the joints, meaning less restriction on carrying out normal activities.
- Treatment with DMARDs should begin as soon as possible after diagnosis.
- DMARDs take several weeks to start working and should be continued indefinitely.
- The treatment of RA requires input from a range of health professionals.

Annex 10

EXAMPLE PATIENT INFORMATION LEAFLET

WHAT IS RHEUMATOID ARTHRITIS (RA)?

RA is a disease that makes your joints become painful, swollen and stiff. This is caused by inflammation taking place in the joints. Inflammation is normally caused by our body's immune system when we are injured or have an infection. We do not know what causes the immune system to cause inflammation in the joints.

HOW IS RA DIAGNOSED?

There is no single test for diagnosing RA. The diagnosis is made from the information you give the doctor as well as the information gained from examining you and the results of blood tests and x-rays.

CAN RA BE CURED?

RA cannot be cured at present, but for many patients it can be controlled.

HOW WILL RA AFFECT ME IN THE FUTURE?

At present it is not possible to predict for an individual person how their RA will affect them in the future. Some people have very mild RA which causes few problems. Others have some pain and stiffness in their joints and occasional flare-ups when their joints become more painful and swollen. This can lead to damage to the joints. Some people will have to modify their activities in some way. A small number of people develop significant problems.

CAN RA BE TREATED?

Yes.

Treatment for RA can:

- help with the pain, stiffness and swelling in joints
- reduce damage to joints
- help people stay able to do all the things they want to.

HOW CAN RA BE TREATED?

Treating RA is a partnership between you, your GP and your rheumatologist. Treatment does not just involve taking tablets. A team of health professionals is also important. These include: nurse specialist, physiotherapist, occupational therapist, pharmacist, dietitian, podiatrist (chiroprapist) and social worker.

You can help by knowing as much as you can about RA and its treatment. If you know about your tests, drugs and the need to watch for side effects, your outlook will be better.

WHEN SHOULD I START TREATMENT FOR RA?

The sooner the better.

The earlier treatment is started the less damage takes place in the joints and the more likely that you will be able to continue your usual activities.

WHAT MEDICATION SHOULD I HAVE?

- **Painkillers** such as paracetamol, cocodamol and coproxamol may help with pain. It is important that you do not take more than the maximum recommended dose. Painkillers other than paracetamol may cause constipation.
- **Nonsteroidal anti-inflammatory drugs (NSAIDs)** such as ibuprofen, diclofenac, naproxen, indomethacin, nabumetone, etodolac, meloxicam, rofecoxib and celecoxib, help with the pain, swelling and stiffness in your joints, but do not stop damage occurring to your joints. There are many different NSAIDs and not all NSAIDs suit everyone. You may have to try several different drugs before you find one that helps you. The main side effect of NSAIDs is indigestion. Sometimes inflammation or ulceration of the stomach or intestine can occur. This may very rarely cause bleeding. If you experience indigestion or have previously had a stomach ulcer you should discuss this with your doctor. Sometimes additional treatment to protect the gastrointestinal tract is needed.
- **Disease modifying anti-rheumatic drugs (DMARDs)** include sulphasalazine, methotrexate, gold, penicillamine, hydroxychloroquine, azathioprine, cyclosporin and leflunomide. You should start on a DMARD as soon as possible after being diagnosed with RA. DMARDs are not painkillers, but over time they should help with the pain and stiffness in your joints and make you feel better. DMARDs are very important because they slow down damage to your joints and reduce disability. DMARDs take some weeks to start working. It is important to continue taking them, even if they do not seem to be working at first. You will be fully informed about the potential risks and benefits of DMARDs. You will be given written information about any DMARD that your doctor has suggested you start. Most DMARDs require regular blood tests and sometimes urine tests in order to look out for side effects. You should be given a card or monitoring sheet on which the results of your blood tests can be recorded.
- **Steroid injections** into joints can help with the pain and swelling in that joint. Rest after injection may result in additional benefit. Sometimes when you have many inflamed joints, steroid will be given as an injection into your muscle.
- **Steroid tablets**, such as prednisolone, are sometimes necessary, but they have potential side effects. They help with symptoms and may prevent joint damage in the short term, but most people who are on steroid tablets for a long time suffer from side effects. These include thinning of bones (osteoporosis), thinning of skin and putting on weight.

HOW LONG SHOULD I CONTINUE ON TREATMENT?

Usually you should stay on treatment with a DMARD for as long as the drug continues to work, provided that you do not develop side effects which are serious or troubling. If this happens then an alternative DMARD will be recommended by your rheumatologist.

Most patients need to keep taking a DMARD in order to stop their arthritis from flaring up and to slow down damage occurring to the joints. Hopefully, if your joint pain improves on the DMARD then you will be able to take fewer painkillers and perhaps stop your NSAID.

SHOULD I EXERCISE OR NOT?

Exercise is important. It can reduce joint pain and stiffness and keep your muscles strong. This will improve your level of fitness and make you feel better. All patients with RA should see a **physiotherapist** for advice about suitable exercises which may be carried out on dry land or in water (hydrotherapy).

SHOULD I CONTINUE TO WORK?

It is important not to make decisions about work too soon. Modern therapy should allow control of your disease and continuation of employment even if hours and activities require modification.

WHAT OTHER TREATMENTS SHOULD I HAVE?

- **Occupational therapists** can advise you about different ways of carrying out many everyday activities. This helps to protect your joints. In addition you can be given simple aids to help with certain tasks.
- Wrist splints can help with pain.
- Footwear is important. Shoes that are comfortable and support your feet are helpful. You can be referred to a **podiatrist** (chiroprapist) and/or orthotist to be supplied with cushioned insoles or better fitting shoes.
- It is helpful if you can be your ideal bodyweight. This is based on your height and your doctor or nurse specialist can advise you about this. A **dietitian** can give you advice about losing weight if you are overweight or putting weight on if you are too thin.

IS THERE A DIET THAT WILL HELP RA?

At present there is no evidence from scientific studies to support changing to any particular diet.

DO ANY HERBAL OR COMPLEMENTARY MEDICINES HELP RA?

Supplements of fish oil may help the symptoms of RA, but do not stop joint damage. Large quantities of fish oil are required. Other complementary medicines have not been shown to be of benefit in RA. Many complementary medicines have not been tested in good quality scientific studies. Complementary medicines may have side effects.

Annex 11

USEFUL ORGANISATIONS/SUPPORT GROUPS

ARTHRITIS RELATED ADDRESSES AND WEBSITES

Arthritis Canada	www.arthritis.ca
Arthritis Care Phoenix House, 7 South Avenue, Clydebank Business Park, Clydebank, G81 2LG Tel: 0141 952 5433 Fax: 0141 952 5433	www.arthritiscare.org.uk
American College of Rheumatology	www.rheumatology.org
Arthritis Foundation of Ireland 1 Clanwilliam Square, Grand Canal Quay, Dublin 2, Ireland Tel: (+353) 01 6618188 Fax: (+353) 01 6618261	www.arthritis-foundation.com
Arthritis Foundation (USA)	www.arthritis.org
Arthritis Research Campaign (ARC) Copeman House, St Mary's Court, St Mary's Gate, Chesterfield, Derbyshire S41 7TD Tel: 01246 558033 Fax: 01246 558007	www.arc.org.uk
British Health Professionals in Rheumatology c/o BSR, 41 Eagle St, London WC1R 4AR Tel: 0171 242 3313 Fax: 0171 242 3277	www.rheumatology.org.uk/BHPR
British Society of Rheumatology 41 Eagle Street, London WC1R 4AR Tel: 020 7 242 3313 Fax: 020 7 242 3277 <i>(includes the British Society for Rheumatology, British Institute of Musculoskeletal Medicine, British Orthopaedic Association, Society for Back Pain Research, the Arthritis and Rheumatism Council for Research)</i>	www.rheumatology.org.uk
European League Against Rheumatism (EULAR) EULAR Secretariat, Witikonstrasse 15, CH-8032 Zürich, Switzerland Tel: +41 1 383 96 90 Fax: +41 1 383 98 10	www.eular.org
The British League against Rheumatism (BLAR) <i>c/o The British Society for Rheumatology (see above)</i>	
International League of Associations for Rheumatology (ILAR)	www.ilar.org
University of Birmingham, Dept of Rheumatology	www.rheuma.bham.ac.uk

OTHER USEFUL ADDRESSES AND WEBSITES

Disabled Living Foundation

380-384 Harrow Rd, London W9 2HU

www.dlf.org.uk

Health information distributed by GPs

www.healthinfocus.co.uk

Health Education Board for Scotland

Woodburn House, Canaan Lane, Edinburgh EH10 4SG

Tel: 0131 536 5500

Fax: 0131 536 5501

www.hebs.scot.nhs.uk

Help for Help Trust (UK)

Highcroft, Romsey Road, Winchester, Hampshire SO22 5DH

Tel: 01962 849100

Fax: 01962 849079

www.hfht.org

provides consumer information and links to health sites

Medical Research Council

MRC Head Office, 20 Park Crescent, London W1N 4AL

Tel: 020 7636 5422

Fax: 020 7436 6179

www.mrc.ac.uk

National Electronic Library for Health

www.nelh.nhs.uk

Organising Medical Networked Information (OMNI)

OMNI / BIOME, Greenfield Medical Library,
Queens Medical Centre, Nottingham NG7 2UH

www.omni.ac.uk

NHS Direct

www.nhsdirect.nhs.uk

UK Health Centre

guide to health/medical information on the internet

www.healthcentre.org.uk/hc/clinic/websites/default.htm

UK reference site for the lay person

www.patient.co.uk

References

- 1 Wolfe F, Zwiilich SH. The long-term outcomes of rheumatoid arthritis: a 23-year prospective, longitudinal study of total joint replacement and its predictors in 1,600 patients with rheumatoid arthritis. *Arthritis Rheum* 1998; 41: 1072-82.
- 2 Pincus T. Rheumatoid arthritis: a medical emergency? *Scand J Rheumatol Suppl* 1994; 100: 21-30.
- 3 Wolfe F. The natural history of rheumatoid arthritis. *J Rheumatol Suppl* 1996; 44: 13-22.
- 4 Young A, Dixey J, Cox N, Davies P, Devlin J, Emery P, et al. How does functional disability in early rheumatoid arthritis (RA) affect patients and their lives? Results of 5 years of follow-up in 732 patients from the Early RA Study (ERAS). *Rheumatol* 2000; 39: 603-11.
- 5 Jantti J, Aho K, Kaarela K, Kautiainen H. Work disability in an inception cohort of patients with seropositive rheumatoid arthritis: a 20 year study. *Rheumatology* 1999; 38: 1138-41.
- 6 Cooper NJ. Economic burden of rheumatoid arthritis: a systematic review. *Rheumatology* 2000; 39: 28-33.
- 7 Emery P. The Roche Rheumatology Prize Lecture. The optimal management of early rheumatoid disease: the key to preventing disability. *Br J Rheumatol* 1994; 33: 765-8.
- 8 Emery P. Therapeutic approaches for early rheumatoid arthritis. How early? How aggressive? *Br J Rheumatol* 1995; 34 (suppl 2): 87-90.
- 9 Machold KP, Eberl G, Leeb BF, Nell V, Windisch B, Smolen JS. Early arthritis therapy: rationale and current approach. *J Rheumatol Suppl* 1998; 53: 13-9.
- 10 Brook A, Corbett M. Radiographic changes in early rheumatoid disease. *Ann Rheum Dis* 1977; 36: 71-73.
- 11 Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. *J Rheumatol* 1989; 16: 585-591.
- 12 Kaarela K, Kautiainen H. Continuous progression of radiological destruction in seropositive rheumatoid arthritis. *J Rheumatol* 1997; 24: 1285-7.
- 13 Graudal NA, Jurik AG, de Carvalho A, Graudal HK. Radiographic progression in rheumatoid arthritis: a long-term prospective study of 109 patients. *Arthritis Rheum* 1998; 41: 1470-1480.
- 14 Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC, Hazes JM. Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. *Arthritis Rheum* 1999; 42: 1854-60.
- 15 Symmons DP, Jones MA, Scott DL, Prior P. Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. *J Rheumatol* 1998; 25: 1072-7.
- 16 Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-324.
- 17 Kirwan JR, Reeback JS. Stanford Health Assessment Questionnaire modified to assess disability in British patients with rheumatoid arthritis. *Br J Rheumatol* 1986; 25: 206-9.
- 18 Pincus T, Brooks RH, Callahan LF. Prediction of long-term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. *Ann Intern Med* 1994; 120: 26-34.
- 19 Wolfe F, Ross K, Hawley DJ, Roberts FK, Cathey MA. The prognosis of rheumatoid arthritis and undifferentiated polyarthritis syndrome in the clinic: a study of 1141 patients. *J Rheumatol* 1993; 20: 2005-9.
- 20 Mitchell DM, Spitz PW, Young DY, Bloch DA, McShane DJ, Fries J. Survival, prognosis and causes of death in Rheumatoid Arthritis. *Arthritis Rheum* 1986; 29: 706-14.
- 21 Devlin J, Gough A, Huissoon A, Perkins P, Holder R, Reece R et al. The acute phase and function in early rheumatoid arthritis. C-reactive protein levels correlate with functional outcome. *J Rheumatol* 1997; 24: 9-13.
- 22 van der Heijde DM, van Riel PL, van Leeuwen MA, van 't Hof MA, van Rijswijk MH, van de Putte LB. Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients. *Br J Rheumatol* 1992; 31: 519-25.
- 23 van Leeuwen MA, van der Heijde DM, van Rijswijk MH, Houtman PM, van Riel PL, van de Putte LB, et al. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts, and acute phase reactants. *J Rheumatol* 1994; 21: 425-9.
- 24 van Schaardenburg D, Hazes JM, de Boer A, Zwinderman AH, Meijers KA, Breedveld FC. Outcome of rheumatoid arthritis in relation to age and rheumatoid factor at diagnosis. *J Rheumatol* 1993; 20: 45-52.
- 25 Paimela L, Palosuo T, Leirisalo-Repo M, Helve T, Aho K. Prognostic value of quantitative measurement of rheumatoid factor in early rheumatoid arthritis. *Br J Rheumatol* 1995; 34: 1146-50.
- 26 Wolfe F, Hawley DJ. Remission in rheumatoid arthritis. *J Rheumatol* 1985; 12: 245-52.
- 27 Corbett M, Dalton S, Young A, Silman A, Shipley M. Factors predicting death, survival and functional outcome in a prospective study of early rheumatoid disease over fifteen years. *Br J Rheumatol* 1993; 32: 717-23.

- 28 Eberhardt KB, Fex E. Functional impairment and disability in early rheumatoid arthritis—development over 5 years. *J Rheumatol* 1995; 22: 1037-42.
- 29 Leigh JP, Fries JF. Predictors of disability in a longitudinal sample of patients with rheumatoid arthritis. *Ann Rheum Dis* 1992; 51: 581-7.
- 30 Callahan LF, Pincus T. Formal education level as a significant marker of clinical status in rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 1346-57.
- 31 Callahan LF, Cordray DS, Wells G, Pincus T. Formal education and five-year mortality in rheumatoid arthritis: mediation by helplessness scale scores. *Arthritis Care Res* 1996; 9: 463-72.
- 32 McEntegart A, Morrison E, Capell HA, Duncan MR, Porter D, Madhok R, et al. Effect of social deprivation on disease severity and outcome in patients with rheumatoid arthritis. *Ann Rheum Dis* 1997; 56: 410-3.
- 33 Maiden N, Capell HA, Madhok R, Hampson R, Thomson EA. Does social disadvantage contribute to the excess mortality in rheumatoid arthritis patients? *Ann Rheum Dis* 1999; 58: 525-9.
- 34 ERAS Study Group. Socioeconomic deprivation and rheumatoid disease: what lessons for the health service? *Ann Rheum Dis* 2000; 59: 794-9.
- 35 Scott DL, Symmons DP, Coulton BL, Popert AJ. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987; 1: 1108-11.
- 36 Fex E, Larsson BM, Nived K, Eberhardt K. Effect of rheumatoid arthritis on work status and social and leisure time activities in patients followed 8 years from onset. *J Rheumatol* 1998; 25: 44-50.
- 37 Capell HA, Murphy EA, Hunter JA. Rheumatoid arthritis: workload and outcome over 10 years. *Q J Med* 1991; 79: 461-76.
- 38 Vliet Vlieland TP, Breedveld FC, Hazes JM. The two-year follow-up of a randomized comparison of in patient multidisciplinary team care and routine out patient care for active rheumatoid arthritis. *Br J Rheumatol* 1997; 36: 82-5.
- 39 Pullar T, Hunter JA, Capell HA. Gold and penicillamine therapy: is shared care with general practitioners effective and safe? *Rheumatol Rehabil*.1982; 21: 139-44.
- 40 Holman HR, Lorig KR. Patient education: essential to good health care for patients with chronic arthritis. *Arthritis Rheum* 1997; 40: 1371-3.
- 41 Barlow JH, Wright CC. Knowledge in patients with rheumatoid arthritis: a longer term follow-up of a randomized controlled study of patient education leaflets. *Br J Rheumatol* 1998; 37: 373-6.
- 42 Superio-Cabuslay E, Ward MM, Lorig KR. Patient education interventions in osteoarthritis and rheumatoid arthritis: a meta-analytic comparison with nonsteroidal anti-inflammatory drug treatment. *Arthritis Care Res* 1996; 9: 292-301.
- 43 Evers AW, Kraaijmaat FW, Geenen R, Bijlsma JW. Psychosocial predictors of functional change in recently diagnosed rheumatoid arthritis patients. *Behav Res Ther* 1998; 36: 179-93.
- 44 Lorig KR, Mazonson PD, Holman HR. Evidence suggesting that health education for self-management in patients with chronic arthritis has sustained health benefits while reducing health care costs. *Arthritis Rheum* 1993; 36: 439-46.
- 45 Kruger JM, Helmick CG, Callahan LF, Haddix AC. Cost-effectiveness of the arthritis self-help course. *Arch Intern Med* 1998; 158: 1245-9.
- 46 Anderson RB, Needleman RD, Gatter RA, Andrews RP, Scarola JA. Patient outcome following inpatient vs. outpatient treatment of rheumatoid arthritis. *J Rheumatol* 1988; 15: 556-60.
- 47 Helewa A, Bombardier C, Goldsmith CH, Menchions B, Smythe HA. Cost-effectiveness of inpatient and intensive outpatient treatment of rheumatoid arthritis. A randomized, controlled trial. *Arthritis Rheum* 1989; 32: 1505-14.
- 48 Lambert CM, Hurst NP, Forbes JF, Lochhead A, Macleod M, Nuki G. Is day care equivalent to inpatient care for active rheumatoid arthritis? Randomised controlled clinical and economic evaluation. *BMJ* 1998; 316: 965-9.
- 49 Yelin E, Wanke LE. An assessment of the annual and long-term direct costs of rheumatoid arthritis: the impact of poor function and functional decline. *Arthritis Rheum* 1999; 42: 1209-18.
- 50 Kobelt G, Eberhardt K, Jonsson L, Jonsson B. Economic consequence of the progression of rheumatoid arthritis in Sweden. *Arthritis Rheum* 1999; 42: 347-56.
- 51 Huskisson EC. Simple analgesics for arthritis. *BMJ* 1974; 4: 196-200.
- 52 Hardin JG Jr, Kirk KA. Comparative effectiveness of five analgesics for the pain of rheumatoid synovitis. *J Rheumatol* 1979; 6: 405 -12.
- 53 Brooks PM, Dougan MA, Mugford S, Meffin E. Comparative effectiveness of 5 analgesics in patients with rheumatoid arthritis and osteoarthritis. *J Rheumatol* 1982; 9: 723-6.
- 54 Emery P, Gibson T. A double-blind study of the simple analgesic nefopam in rheumatoid arthritis. *Br J Rheumatol* 1986; 25: 72 -6.
- 55 Seideman P, Melander A. Equianalgesic effects of paracetamol and indomethacin in rheumatoid arthritis. *Br J Rheumatol* 1988; 27: 117-22.
- 56 Furst DE. Are there differences among nonsteroidal anti-inflammatory drugs? Comparing acetylated salicylates, nonacetylated salicylates, and nonacetylated nonsteroidal anti-inflammatory drugs. *Arthritis Rheum* 1994; 37: 1-9.

- 57 Brooks PM, Day RO. Nonsteroidal anti-inflammatory drugs—differences and similarities. *N Engl J Med* 1991; 324: 1716-25.
- 58 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. No 40 (September 2000). NSAID Interactions. Appendix I: Interactions. 588-624. London: BMA, RPS, 2000.
- 59 Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *NEJM* 1999; 340: 1888-99.
- 60 Fries JF, Spitz PW, Williams CA, Bloch DA, Singh G, Hubert HB. A toxicity index for comparison of side effects among different drugs. *Arthritis Rheum* 1990; 33: 121-30.
- 61 Morris AJ, Madhok R, Sturrock RD, Capell HA, MacKenzie JF. Enteroscopic diagnosis of small bowel ulceration in patients receiving non-steroidal anti-inflammatory drugs. *Lancet* 1991; 337: 520.
- 62 Scottish Intercollegiate Guidelines Network. *Helicobacter pylori*: eradication in dyspeptic disease. Edinburgh: SIGN 1996 (SIGN Publication No. 8).
- 63 Langman MJ, Weil J, Wainwright P, Lawson DH, Rawlins MD, Logan RF et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; 343: 1075-8.
- 64 Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; 343: 1048.
- 65 Hawkey CJ, Karrasch JA, Szczepanski L, Walker DG, Barkun A, Swannell AJ et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. *NEJM* 1998; 338: 727-34.
- 66 Silverstein FE, Graham DY, Senior JR, Davies HW, Stuthers BJ, Bittman RM et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1995; 123: 241-9.
- 67 Swan SK, Rudy DW, Lasseter KC, Ryan CF, Buechel KL, Lambrecht LJ, et al. Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low salt diet. A randomized controlled trial. *Ann Intern Med* 2000; 133:1-9.
- 68 Simon LS, Weaver AL, Graham DY, Kivitz AJ, Lipsky PE, Hubbard RC et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomised controlled trial. *JAMA* 1999; 282: 1921-8.
- 69 Emery P, Zeidler H, Kvien TK, Guslandi M, Naudin R, Stead H et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet* 1999; 354: 2106-11.
- 70 Bensen WG, Zhao SZ, Burke TA, Zabinski RA, Makuch RW, Maurath CJ, et al. Upper gastrointestinal tolerability of celecoxib, a COX-2 specific inhibitor, compared to naproxen and placebo. *J Rheumatol* 2000; 27: 1876-83.
- 71 Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS Study: a randomized controlled trial. *JAMA* 2000; 284: 1247-55.
- 72 Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B et al for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of Rofecoxib and Naproxen in patients with rheumatoid arthritis. *NEJM* 2000; 343: 1520-8.
- 73 Committee on Safety in Medicines and The Medicines Control Agency. Current problems in pharmaco-vigilance. September 2000; 26: 13.
- 74 Schnitzer TJ, Truitt K, Fleischmann R, Dalgin P, Block J, Zeng Q, et al. The safety profile, tolerability, and effective dose range of rofecoxib in the treatment of rheumatoid arthritis. Phase II Rofecoxib Rheumatoid Arthritis Study Group. *Clin Ther* 1999; 21: 1688-702.
- 75 Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of two metaanalyses. *Arthritis Rheum* 1990; 33: 1449-61.
- 76 Felson DT, Anderson JJ, Meenan RF. Use of short-term efficacy /toxicity tradeoffs to select second-line drugs in rheumatoid arthritis. A metaanalysis of published clinical trials. *Arthritis Rheum* 1992; 35: 1117-25.
- 77 Andrews FM, Golding DN, Freeman AM et al. Controlled trial of D (-) penicillamine in severe rheumatoid arthritis. *Lancet* 1973; 1: 275-80.
- 78 Clark P, Casas E, Tugwell P, Medina C, Gheno C, Tenorio G et al. Hydroxychloroquine compared with placebo in rheumatoid arthritis. A randomized controlled trial. *Ann Intern Med* 1993; 119: 1067-71.
- 79 Golding JR, Andrews FM, Camp V, Day AT, Freeman AM, Golding DN et al. A randomised trial of hydroxychloroquine in early rheumatoid arthritis: the HERA study. *Am J Med* 1995; 98: 156-68.
- 80 Jessop JD, O'Sullivan MM, Lewis PA, Williams LA, Camilleri JP, Plant MJ et al. A long-term five-year randomized controlled trial of hydroxychloroquine, sodium aurothiomalate, auranofin and penicillamine in the treatment of patients with rheumatoid arthritis. *Br J Rheumatol* 1998; 37: 992-1002.

- 81 Munro R, Hampson R, McEntegart A, Thomson EA, Madhok R, Capell H. Improved functional outcome in patients with early rheumatoid arthritis treated with intramuscular gold: results of a five year prospective study. *Ann Rheum Dis* 1998; 57: 88-93.
- 82 Dijkmans BA, van Rijthoven AW, Goei The HS, Boers M, Cats A. Cyclosporine in rheumatoid arthritis. *Semin Arthritis Rheum* 1992; 22: 30-6.
- 83 Fries JF, Williams CA, Morfeld D, Singh G, Sibley J. Reduction in long-term disability in patients with rheumatoid arthritis by disease modifying anti-rheumatic drug-based treatment strategies. *Arthritis Rheum* 1996; 39: 616-22.
- 84 Borg G, Allander E, Lund B, Ber E, Brodin U, Pettersson H et al. Auranofin improves outcome in early rheumatoid arthritis. Results from a 2-year, double blind, placebo controlled study. *Journal of Rheumatology* 1988; 15: 1747-54.
- 85 Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. *European Leflunomide Study Group. Lancet* 1999; 353: 259-66.
- 86 Egsmose C, Lund B, Borg G, Pettersson H, Berg E, Brodin U et al. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup of a prospective double blind placebo controlled study. *J Rheumatol* 1995; 22: 2208-13.
- 87 van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, van der Veen MJ et al. The effectiveness of early treatment with "second line" antirheumatic drugs. A randomized, controlled trial. *Ann Intern Med* 1996; 124: 699-707.
- 88 Tsakonas E, Fitzgerald AA, Fitzcharles MA, Cividino A, Thorne JC, M'Seffar A et al. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year follow up on the hydroxychloroquine in early rheumatoid arthritis (HERA) study. *J Rheumatol* 2000; 27: 623-9.
- 89 van Jaarsveld CH, Jacobs JW, van der Veen MJ, Blaauw AA, Kruize AA, Hofman DM, et al. Aggressive treatment in early rheumatoid arthritis: a randomised controlled trial. On behalf of the Rheumatic Research Foundation Utrecht, The Netherlands. *Ann Rheum Dis* 2000; 59: 468-77.
- 90 Stenger AA, Van Leeuwen MA, Houtman PM, Bruyn GA, Speerstra F, Barendsen BC et al. Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. *Br J Rheumatol* 1998;37:1157-63.
- 91 Zeidler HK, Kvien TK, Hannonen P, Wollheim FA, Forre O, Geidel H et al. Progression of joint damage in early active severe rheumatoid arthritis during 18 months of treatment: comparison of low-dose cyclosporin and parenteral gold. *Br J Rheumatol* 1998; 37: 874-82.
- 92 McEntegart A, Porter D, Capell HA, Thomson EA. Sulfasalazine has a better efficacy/toxicity profile than auranofin – evidence from a 5 year prospective randomized trial. *J Rheumatol* 1996; 23: 1887-90.
- 93 van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, van de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989; 1: 1036-8.
- 94 Menninger H, Herborn G, Sander O, Blechschmidt J, Rau R. A 36 month comparative trial of methotrexate and gold sodium thiomalate in the treatment of early active and erosive rheumatoid arthritis. *Br J Rheumatol* 1998; 37: 1060-8.
- 95 Rau R, Herborn G, Menninger M, Sangha O. Progression in early erosive rheumatoid arthritis: 12 month results from a randomised controlled trial comparing methotrexate and gold sodium thiomalate. *Br J Rheumatol* 1998; 37: 1220-6.
- 96 Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Leflunomide Rheumatoid Arthritis Investigators Group. Arch Intern Med* 1999; 159: 2542-50.
- 97 ten Wolde S, Breedveld FC, Hermans J, Vandenbroucke JP, van de Laar MA, Markkuse HM et al. Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis. *Lancet* 1996; 347: 347-52.
- 98 Gotzsche PC, Hansen M, Stoltenberg M, Svendsen A, Beier J, Faarvang KL et al. Randomized, placebo controlled trial of withdrawal of slow-acting antirheumatic drugs and of observer bias in rheumatoid arthritis. *Scan J Rheumatol* 1996; 25: 194-9.
- 99 Sokka T, Hannonen P. Utility of disease modifying antirheumatic drugs in "sawtooth" strategy. A prospective study of early rheumatoid arthritis patients up to 15 years. *Ann Rheum Dis* 1999; 58: 618-22.
- 100 Fries JF. ARAMIS and toxicity measurement. (Arthritis Rheumatism and Aging Medical Information System). *J Rheumatol* 1995; 22: 995-7.
- 101 Beauparlant P, Papp K, Haraoui B. The incidence of cancer associated with the treatment of rheumatoid arthritis. *Semin Arthritis Rheum* 1999; 29: 148-58.
- 102 Baecklund E, Ekblom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. *BMJ* 1998; 317: 180-1.
- 103 Asten P, Barrett J, Symmons D. Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases. *J Rheumatol* 1999; 26: 1705-14.
- 104 Furst DE, Lindsley H, Baethge B, Botstein GR, Caldwell J, Dietz F et al. Dose-loading with hydroxychloroquine improves the rate of response in early, active rheumatoid arthritis: a randomized, double-blind six-week trial with eighteen-week extension. *Arthritis Rheum* 1999; 42: 357-65.
- 105 A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA Study. *Am J Med* 1995; 98: 156-68.
- 106 Capell HA. Clinical efficacy of sulphasalazine - a review. *Br J Rheumatol* 1995; 34: 35-9.

- 107 Weinblatt ME, Reda D, Henderson W, Giobbie-Hurder A, Williams D, Diani A et al. Sulfasalazine treatment for rheumatoid arthritis: a metaanalysis of 15 randomized trials. *J Rheumatol* 1999; 26: 2123-30.
- 108 Box SA, Pullar T. Sulphasalazine in the treatment of rheumatoid arthritis. *Br J Rheumatol* 1997; 36: 382-6.
- 109 Alarcon GS, Tracy IC, Strand GM, Singh K, Macaluso M. Survival and drug discontinuation analyses in a large cohort of methotrexate treated rheumatoid arthritis patients. *Ann Rheum Dis* 1995; 54: 708-12.
- 110 van Ede AE, Laan RF, Blom HJ, De Abreu RA, van de Putte LB. Methotrexate in rheumatoid arthritis: an update with focus on mechanisms involved in toxicity. *Semin Arthritis Rheum* 1998; 27: 277-92.
- 111 Furst DE. The rational use of methotrexate in rheumatoid arthritis and other rheumatic diseases. *Br J Rheumatol* 1997; 36: 1196-204.
- 112 Suarez-Almazor ME, Spooner C, Belseck E. Penicillamine for rheumatoid arthritis (Cochrane Review). In: *The Cochrane Library Issue 2, 2000*. Oxford: Update Software.
- 113 Suarez-Almazor ME, Spooner C, Belseck E. Azathioprine for rheumatoid arthritis. (Cochrane Review). In: *The Cochrane Library Issue 2, 2000*. Oxford: Update Software.
- 114 Emery P, Breedveld FC, Lemmel EM, Kaltwasser JP, Dawes PT, Gomor B, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatol* 2000; 39: 655-65.
- 115 Chaudhuri K, Torley N, Madhok R. Disease-modifying anti-rheumatic drugs. Cyclosporin. *Br J Rheumatol* 1997; 36: 1016-21.
- 116 Ocular toxicity and hydroxychloroquine: guidelines for screening (replacing RCOphth Guidelines 1993). London: Royal College of Ophthalmologists; 1998.
- 117 British Society for Rheumatology. National guidelines for the monitoring of second line drugs. London: The Society; 2000.
- 118 Hydroxychloroquine datasheet. Electronic Medicines Compendium (ABPI). <http://emc.vhn.net/public>
- 119 Bluhm GB, Sharp JT, Tilley BC, Alarcon GS, Cooper SM, Pillemer SR et al. Radiographic results from the Minocycline in Rheumatoid Arthritis (MIRA) Trial. *J Rheumatol* 1997; 24: 1295-302.
- 120 Kloppenburg M, Breedveld FC, Terwiel JP, Mallee C, Dijkmans BA. Minocycline in active rheumatoid arthritis. A double-blind, placebo-controlled trial. *Arthritis Rheum* 1994; 37:629-36.
- 121 Tilley BC, Alarcon GS, Heyse SP, Trentham DE, Neuner R, Kaplan DA et al. Minocycline in rheumatoid arthritis. A 48-week, double-blind, placebo-controlled trial. MIRA Trial Group. *Ann Intern Med* 1995; 122:81-9.
- 122 O'Dell JR, Paulsen G, Haire CE, Blakely K, Palmer W, Wees S et al. Treatment of early seropositive rheumatoid arthritis with minocycline: four-year followup of a double-blind, placebo-controlled trial. *Arthritis Rheum* 1999;42: 1691-5.
- 123 Ortiz Z, Shea B, Suarez-Almazor ME, Moher D, Wells GA, Tugwell P. The efficacy of folic acid and folinic acid in reducing methotrexate gastrointestinal toxicity in rheumatoid arthritis. A metaanalysis of randomized controlled trials. *J Rheumatol* 1998; 25: 36-43.
- 124 Sokka T, Mottonen T, Hannonen P. Disease-modifying anti-rheumatic drug use according to the 'sawtooth' treatment strategy improves the functional outcome in rheumatoid arthritis: results of a long-term follow-up study with review of the literature. *Rheumatology* 2000; 39: 34-42.
- 125 Felson DT, Anderson JJ, Meenan RF. The efficacy and toxicity of combination therapy in rheumatoid arthritis. A meta-analysis. *Arthritis Rheum* 1994; 37: 1487-91.
- 126 Willkens RF, Sharp JT, Stablein D, Marks C, Wortmann R. Comparison of azathioprine, methotrexate, and the combination of the two in the treatment of rheumatoid arthritis. A forty-eight-week controlled clinical trial with radiologic outcome assessment. *Arthritis Rheum* 1995; 38: 1799-806.
- 127 Faarvang KL, Egsmose C, Kryger P, Podenphant J, Ingeman-Nielsen M, Hansen TM. Hydroxychloroquine and sulphasalazine alone and in combination in rheumatoid arthritis: a randomised double blind trial. *Ann Rheum Dis* 1993; 52: 711-5.
- 128 O'Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications *NEJM* 1996; 334: 1287-91.
- 129 Haagsma CJ, van Riel PL, de Jong AJ, van de Putte LB. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. *Br J Rheumatol* 1997; 36: 1082-8.
- 130 Dougados M, Combe B, Cantagrel A, Goupille P, Olive P, Schattenkirchner M et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 1999; 58: 22-5.
- 131 Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 1999; 353: 1568-73.

- 132 Porter DR, Capell HA, Hunter J. Combination therapy in rheumatoid arthritis—no benefit of addition of hydroxychloroquine to patients with a suboptimal response to intramuscular gold therapy. *J Rheumatol.* 1993; 20: 645-9.
- 133 Tugwell P, Pincus T, Yocum D, Stein M, Gluck O, Kraag G et al. Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. The Methotrexate-Cyclosporine Combination Study Group. *NEJM* 1995; 333: 137-41.
- 134 Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999 Dec 4; 354: 1932-9.
- 135 Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *NEJM* 1999; 340: 253-9.
- 136 Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *NEJM* 2000; 343: 1594-1602.
- 137 Boers M, Verhoeven AC, Markuse HM, van de Laar MA, Westhovens R, van Denderen JC et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997; 350: 309-18.
- 138 Proudman SM, Conaghan PG, Richardson C, Griffiths B, Green MJ, McGonagle RJ, et al. Treatment of poor prognosis early rheumatoid arthritis: a randomized study of treatment with methotrexate, cyclosporin a, and intraarticular corticosteroids compared with sulfasalazine alone. *Arthritis Rheum* 2000; 43: 1809-19.
- 139 Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *NEJM* 2000; 343: 1586-93.
- 140 Seror P, Pluvinage P, d'Andre FL, Benamou P, Attuil G. Frequency of sepsis after local corticosteroid injection (an inquiry on 1160000 injections in rheumatological private practice in France). *Rheumatology* 1999; 38: 1272-4.
- 141 Weitoft T, Uddenfeldt P. Importance of synovial fluid aspiration when injecting intra-articular corticosteroids. *Ann Rheum Dis* 2000; 59: 233-5.
- 142 Chakravarty K, Pharoah PD, Scott DG. A randomized controlled study of post-injection rest following intra-articular steroid therapy for knee synovitis. *Br J Rheumatol* 1994; 33: 464-8.
- 143 Laan RF, Jansen TL, van Riel PL. Glucocorticosteroids in the management of rheumatoid arthritis. *Rheumatology* 1999; 38: 6-12.
- 144 Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. *NEJM* 1995; 333: 142-6.
- 145 Million R, Kellgren JH, Poole P, Jayson MI. Long-term study of management of rheumatoid arthritis. *Lancet* 1984; 1: 812-6.
- 146 Hickling P, Jacoby RK, Kirwan JR. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. *Br J Rheumatol* 1998; 37: 930-6.
- 147 Baltzan MA, Suissa S, Bauer DC, Cummings SR. Hip fractures attributable to corticosteroid use. Study of Osteoporotic Fractures Group. *Lancet* 1999 17; 353: 1327.
- 148 Committee on Safety in Medicines and the Medicines Control Agency. Current problems in pharmacovigilance. London: The Committee; 2000. v.26, p.13.
- 149 Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA et al. The mortality of rheumatoid arthritis. *Arthritis Rheumatol* 1994; 37: 481-94.
- 150 McDougall R, Sibley J, Haga M, Russell A. Outcome in patients with rheumatoid arthritis receiving prednisone compared to matched controls. *J Rheumatol* 1994; 21: 1207-13.
- 151 Saag KG, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, Zimmerman B et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. *Am J Med* 1994; 96: 115-23.
- 152 Saag KG. Low-dose corticosteroid therapy in rheumatoid arthritis: balancing the evidence. *Am J Med* 1997; Dec 29103(6A): 31S-39S.
- 153 Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997; 350: 834-43.
- 154 Andrade LE, Ferraz MB, Atra E, Castro A, Silva MS. A randomized controlled trial to evaluate the effectiveness of homeopathy in rheumatoid arthritis. *Scand J Rheum* 1991; 20: 204-8.
- 155 Gibson RG, Gibson SL, MacNeill AD, Buchanan WW. Homoeopathic therapy in rheumatoid arthritis: evaluation by double-blind clinical therapeutic trial. *Br J Clin Pharmacol* 1980; 9: 453-9.
- 156 Mills SY, Jacoby RK, Chacksfield M, Willoughby M. Effect of a proprietary herbal medicine on the relief of chronic arthritic pain: a double-blind study. *Br J Rheumatol* 1996; 35: 874-8.
- 157 Patrick M, Heptinstall S, Doherty M. Feverfew in rheumatoid arthritis: a double blind, placebo controlled study. *Ann Rheum Dis* 1989; 48: 547-9.

- 158 Bhatt- Saunders D. Acupuncture for rheumatoid arthritis: an analysis of the literature. *Semin Arthritis Rheum* 1985; 4: 225-31.
- 159 David J, Townsend S, Sathanathan R, Kriss S, Dore CJ. The effect of acupuncture on patients with rheumatoid arthritis: a randomised, placebo-controlled cross-over study. *Rheumatology* 1999; 38: 864-9.
- 160 Huskisson EC, Scott J, Bryans R. Seatone is ineffective in RA. *BMJ* 1981; 282: 1358-9.
- 161 Larkin JG, Capell HA, Sturrock RD. Seatone in rheumatoid arthritis: a six-month placebo-controlled study. *Ann Rheum Dis* 1985; 44: 199-201.
- 162 Tarp U, Overvad K, Thorling EB, Graudal H, Hansen JC. Selenium treatment in rheumatoid arthritis. *Scand J Rheumatol* 1985; 14: 364-8.
- 163 Ernst E. Evidence-based complementary medicine: a contradiction in terms? *Ann Rheum Dis* 1999; 58: 69-70.
- 164 MacDonald AG, Murphy EA, Capell HA, Bankowska UZ, Ralston SH. Effects of hormone replacement therapy in rheumatoid arthritis: a double blind placebo-controlled study. *Ann Rheum Dis* 1994; 53: 54-7.
- 165 Hall GM, Daniels M, Huskisson EC, Spector TD. A randomised controlled trial of the effect of hormone replacement therapy on disease activity in postmenopausal rheumatoid arthritis. *Ann Rheum Dis* 1994; 53: 112-6.
- 166 Hall GM, Daniels M, Doyle DV, Spector TD. Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. *Arthritis Rheum* 1994; 37: 1499-505.
- 167 Helewa A, Goldsmith CH, Lee P, Bombardier C, Hanes B, Smythe HA et al. Effects of occupational therapy home service on patients with rheumatoid arthritis. *Lancet* 1991; 337: 1453-6.
- 168 Hammond A, Lincoln N, Sutcliffe L. A crossover trial evaluating an educational-behavioural joint protection programme for people with rheumatoid arthritis. *Patient Educ Couns* 1999; 37: 19-32.
- 169 Bell MJ, Lineker SC, Wilkins AL, Goldsmith CH, Badley EM. A randomized controlled trial to evaluate the efficacy of community based physical therapy in the treatment of people with rheumatoid arthritis. *J Rheumatol* 1998; 25: 231-7.
- 170 Van den Ende CHM, Vliet Vlieland TPM, Munneke M, Hazes JMW. Dynamic exercise therapy for rheumatoid arthritis (Cochrane Review) In: *The Cochrane Library Issue 2, 2000*. Oxford: Update Software.
- 171 Bostrom C, Harms-Ringdahl K, Karreskog H, Nordemar R. Effects of static and dynamic shoulder rotator exercises in women with rheumatoid arthritis: a randomised comparison of impairment, disability, handicap, and health. *Scand J Rheumatol* 1998; 27: 281-90.
- 172 Ahern M, Nicholls E, Simionetta E, Clark M, Bond M. Clinical and physiological effects of hydrotherapy in rheumatic diseases. *Clin Rehab* 1995; 9: 204-12.
- 173 Hall J, Skevington SM, Maddison PJ, Chapman K. A randomized and controlled trial of hydrotherapy in rheumatoid arthritis. *Arthritis Care Res* 1996; 9: 206-15.
- 174 Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Knipschild PG. Taking baths: the efficacy of balneotherapy in patients with arthritis. A systematic review. *J Rheumatol* 1997; 24: 1964-71.
- 175 Ayling J, Marks, R. Efficacy of paraffin wax baths for rheumatoid arthritic hands. *Physiotherapy* 2000; 86: 190-201.
- 176 Goats GC, Hunter JA, Flett E, Stirling A. Low intensity laser and phototherapy for rheumatoid arthritis. *Physiotherapy* 1996; 82: 311-20.
- 177 Hall J, Clarke AK, Elvins DM, Ring EF. Low level laser therapy is ineffective in the management of rheumatoid arthritic finger joints. *Br J Rheumatol* 1994; 33: 142-7.
- 178 Heussler JK, Hinchey G, Margiotta E, Quinn R, Butler P, Martin J et al. A double blind randomised trial of low power laser treatment in rheumatoid arthritis. *Ann Rheum Dis* 1993; 52: 703-6.
- 179 Palmgren N, Jensen GF, Kaae K, Windelin M, Colohov HC. Low-power laser therapy in rheumatoid arthritis. *Lasers in Medical Science* 1989; 4: 193-6.
- 180 Konrad K. Randomised double blind placebo controlled study of ultrasonic treatment of the hands of rheumatoid arthritis patients. *European Journal of Physical Medicine & Rehabilitation* 1994; 4: 155-7.
- 181 Feinberg J. Effect of the arthritis health professional on compliance with use of resting hand splints by patients with rheumatoid arthritis. *Arthritis Care Res* 1992; 5: 17-23.
- 182 Callinan NJ, Mathiowetz V. Soft versus hard resting hand splints in rheumatoid arthritis: pain relief, preference, and compliance. *Am J Occup Ther* 1996; 50: 347-53.
- 183 Kjekouk I, Moller G, Kvien TK. Use of commercially produced elastic wrist orthoses in chronic arthritis: a controlled study. *Arthritis Care Res* 1995; 8: 108-13.
- 184 Pagnotta A, Baron M, Korner-Bitensky N. The effect of a static wrist orthosis on hand function in individuals with rheumatoid arthritis. *J Rheumatol* 1998; 25: 879-85.
- 185 Stern EB, Ytterberg SR, Krug HE, Mahowald ML. Finger dexterity and hand function: effect of three commercial wrist extensor orthoses on patients with rheumatoid arthritis. *Arthritis Care Res* 1996; 9: 197-205.
- 186 Stern EB, Ytterberg SR, Krug HE, Mullin GT, Mahowald ML. Immediate and short-term effects of three commercial wrist extensor orthoses on grip strength and function in patients with rheumatoid arthritis. *Arthritis Care Res* 1996; 9: 42-50.

- 187 Locke M, Perry J, Campbell J Thomas L. Ankle and subtalar motion during gait in arthritic patients. *Phys Ther* 1984; 64: 504-9.
- 188 MacSween A, Brydson G, Hamilton J. The effect of custom moulded ethyl vinyl acetate foot orthoses on the gait of patients with rheumatoid arthritis. *Foot* 1999; 9:128-3.
- 189 Hodge MC, Bach TM, Carter MG. Novel Award First Prize Paper. Orthotic management of plantar pressure and pain in rheumatoid arthritis. *Clinical Biomechanics* 1999; 14: 567-75.
- 190 Scottish Intercollegiate Guidelines Network. Obesity in Scotland: integrating prevention and weight management. Edinburgh: SIGN 1996 (SIGN Publication No. 8).
- 191 Munro R, Capell HC. Prevalence of low body mass in rheumatoid arthritis: association with the acute phase response. *Ann Rheum Dis* 1997; 56: 326-9.
- 192 Helliwell M, Coombes EJ, Moody BJ, Batstone GF, Robertson JC. Nutritional status in patients with Rheumatoid Arthritis. *Ann Rheum Dis* 1984; 43: 386-90.
- 193 Haugen M, Fraser D, Forre O. Diet therapy for the patient with rheumatoid arthritis? *Rheumatology* 1999; 38: 1039-44.
- 194 Kjeldsen-Kragh J, Haugen M, Borchgrevink CF, Laerum E, Eek M, Mowinkel P et al. Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. *Lancet* 1991; 338: 899-902.
- 195 Fortin P, Lew RA, Liang MH, Wright EA, Beckett LA, Chalmers TC et al. Validation of a meta-analysis: The effects of fish oil in Rheumatoid Arthritis. *J Clin Epidemiol* 1995; 48: 1379-90.
- 196 Brezeski M. Evening primrose oil in patients with rheumatoid arthritis and side-effects of non-steroidal anti-inflammatory drugs. *Br J Rheum* 1991; 30: 370-2.
- 197 Leventhal LJ, Boyce EG, Zurier RB. Treatment of rheumatoid arthritis with blackcurrant seed oil. *Br J Rheum* 1994; 33: 847-52.
- 198 Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definitions of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 727-35.
- 199 van Gestel AM, Prevoo ML, van't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. *Arthritis Rheum* 1996; 39: 34-40.
- 200 Ritchie DM, Boyle JA, McInnes JM, Jasani MK, Dalakos TG, Grieveson P, et al. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Q J Med* 1968; 37: 393-406.
- 201 Sharp JT. An overview of radiographic analysis of joint damage in rheumatoid arthritis and its use in meta analysis. *J Rheumatol* 2000; 27: 254-60.
- 202 Kirwan J. Using the Larsen index to assess radiographic progression in rheumatoid arthritis. *J Rheumatol* 2000; 27: 264-8.

Update to printed guideline

11 Oct 2004

Withdrawal of Rofecoxib

The NSAID Rofecoxib is mentioned in Section 4.2.4 and Annex 10 of this guideline. This drug has been voluntarily withdrawn from the market by the manufacturers due to concerns about a possible increased risk of heart attack or stroke. Patients currently being prescribed Rofecoxib should be transferred to a suitable alternative NSAID. Further information about the reasons for withdrawal of the drug can be found on the US Federal Drug Administration Web site at <http://www.fda.gov/medwatch/SAFETY/2004/safety04.htm#vioxx>

Quick Reference Guide

CLINICAL FEATURES OF EARLY RHEUMATOID ARTHRITIS (RA)

Symptoms

- Joint pain/swelling
- Stiffness following inactivity
- Systemic 'flu-like' features

Signs

- Synovitis
- Joint swelling/tenderness
- Extra-articular features

INFLAMMATORY POLYARTHRITIS

Differential diagnosis

- Viral arthritis
- Reactive arthritis
- Seronegative spondyloarthropathy
- Connective tissue disease
- Polymyalgia rheumatica
- Polyarticular gout
- Fibromyalgia
- Medical conditions presenting with arthropathy

Helpful investigations

- Erythrocyte sedimentation rate (ESR) /C-reactive protein (CRP)
- Full blood count
- Urea & electrolytes
- Liver function tests
- Uric acid/synovial fluid analysis
- Urinalysis
- Rheumatoid factor
- Anti-nuclear antibody
- Radiology

Adverse prognostic features in early RA

- Many active joints
- High ESR or CRP at outset
- Positive rheumatoid factor
- Early radiological erosions
- Poorer scores of function at outset
- Adverse socio-economic circumstances and lower educational level

EARLY INITIATION OF TREATMENT

- B** RA should be treated as early as possible with disease modifying anti-rheumatic drugs (DMARDs) to control symptoms and delay disease progression.
- All patients with persistent inflammatory joint disease (>6-8 weeks duration) already receiving simple analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) should be considered for referral for specialist rheumatology opinion and DMARD therapy, preferably within 12 weeks.

THE ROLE OF THE MULTIDISCIPLINARY TEAM

- All patients with early RA should have access to a range of health professionals, including general practitioner, rheumatologist, nurse specialist, physiotherapist, occupational therapist, dietitian, podiatrist, pharmacist and social worker.
- C** Skilled occupational therapy advice should be available to those experiencing limitations in function.
- C** Resting and working splints can be used to provide pain relief.
- B** Patients should be encouraged to undertake simple dynamic exercises.
- Podiatry referral should be offered to all patients.

PHARMACOLOGICAL MANAGEMENT OF EARLY RA

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

B The lowest NSAID dose compatible with symptom relief should be prescribed. NSAIDs should be reduced and if possible withdrawn when a good response to DMARDs is achieved.

B Introduce gastro-protection in RA patients >65 years and in those with a past history of peptic ulcer.

- Simple analgesics should be used in place of NSAIDs if possible and DMARDs should be introduced early to suppress disease activity.
 - Only one NSAID should be prescribed at a time.
 - Prescribers should be aware of the many potential interactions with NSAIDs and the side effect profiles of different drugs.
 - Consider intra-articular corticosteroids, particularly when disease is localised.
 - NSAIDs should be avoided in patients taking anticoagulants or corticosteroids.

DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)

B Early DMARD therapy in RA is important to maintain function and reduce later disability.

B DMARD therapy should be sustained in inflammatory disease in order to maintain disease suppression.

- DMARD choice should take into account patient preference and existing co-morbidity.

B Sulphasalazine, methotrexate, IM gold, and penicillamine are equally effective DMARDs.

B Sulphasalazine and methotrexate are the current DMARDs of choice due to their more favourable efficacy/toxicity profiles.

B At present the balance of evidence does not support the routine use of combination DMARD therapy in early RA.

- Patients should be counselled about the benefits and risks of specific DMARDs, and should be provided with additional written information.
- Clear advice about monitoring of specific DMARDs should be available to the patient, GP and practice nurse.

CORTICOSTEROID THERAPY

B Oral corticosteroids are not recommended for routine use, as there is no sustained clinical or functional benefit and there is high risk of toxicity with long term use.

D The lowest possible dose of corticosteroid should be used for the shortest possible time.

D Monitor patients closely for adverse corticosteroid effects. Be alert to the possibility of diabetes, cataract and infection. Inform patients not previously infected of the danger of chicken pox/shingles exposure.

- Inform patients of the risks of corticosteroids prior to prescription and issue a steroid warning card.

© Scottish Intercollegiate Guidelines Network, 2000
Derived from the national clinical guideline recommended for use in Scotland by the
Scottish Intercollegiate Guidelines Network (SIGN)
Royal College of Physicians of Edinburgh, 9 Queen Street, Edinburgh EH2 1JQ

**This guideline was issued in December 2000 and will be reviewed in 2002.
Available on the SIGN website: www.sign.ac.uk**